UNITED STATES OF AMERICA

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FOOD AND DRUG ADMINISTRATION

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CENTER FOR DRUG EVALUATION AND RESEARCH

ARTHRITIS ADVISORY COMMITTEE

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FAST ONSET OF PAIN RELIEF/
CHRONIC AND ACUTE PAIN CLAIM STRUCTURE

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WEDNESDAY

MARCH 25, 1998

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The advisory committee met in Salons A, B, C and D at the Gaithersburg Hilton, 620 Perry Parkway, Gaithersburg, Maryland, at 8:00 a.m., Dr. Michelle Petri, Chairman of the Committee, presiding.

PRESENT:

MICHELLE PETRI, M.D., MPH	Chairman
MATTHEW H. LIANG, M.D., MPH	Member
LEE S. SIMON, M.D.	Member
LEONA M. MALONE	Consumer Representative
FRANK PUCINO, JR. Pharm. D.	Member
BARBARA C. TILLEY, Ph.D.	Member
NIGEL E. HARRIS, M.D.	Member
DAVID E. YOCUM, M.D.	Member
KENNETH D. BRANDT, M.D.	Consultant
LEIGH F. CALLAHAN, Ph.D.	Consultant
FELIX FERNANDEZ-MADRID, M.D., Ph.D.,	Consultant
LARRY W. MORELAND, M.D.	Consultant
THEODORE G. TONG, Pharm.D.	NDAC
PATRICIA A. McGRATH, Ph.C.	NDAC
LYNN McKINLEY-GRANT, M.D.	NDAC
MARY A. KODA-KIMBLE, Pharm.D.	NDAC

PRESENT: (continued)

GEORGE A. BLEWITT, M.D.,	NDAC Industry Representative
MITCHELL B. MAX, M.D.	SGE Consultant
EUGENE LASKA, Ph.D.	Guest Expert
KATHLEEN REEDY	Executive Secretary

ALSO PRESENT:

MICHAEL WEINTRAUB, M.D.	FDA
JOHN E. HYDE, M.D., Ph.D.	FDA
LINDA KATZ, M.D., MPH	FDA

I-N-D-E-X

P-R-O-C-E-E-D-I-N-G-S

(8:08 a.m.)

CHAIRMAN PETRI: Good morning. My name is Michelle Petri. I want to welcome you to the Arthritis Advisory Committee.

Today we have representation from Nonprescription Drugs. I'd like to start with our introduction, and I have a habit of starting on the right.

DR. WEINTRAUB: Thank you, Michelle. My name is Michael Weintraub. I'm the Director of Office of Drug Evaluation Number 5 and Acting Director of the Arthritis and Analgesic and Ophthalmologic Division.

DR. HYDE: Hi. I'm John Hyde, Acting Deputy for Analgesic Anti-inflammatory Drugs.

DR. BRANDT: I'm Ken Brandt. I'm a rheumatologist from Indiana University.

DR. McKINLEY-GRANT: I'm Lynn McKinley-Grant. I'm a dermatologist in Washington, D.C., and a member of the Nonprescription Drug Advisory Committee.

DR. TONG: Good morning. I'm Ted Tong. I am a professor of pharmacy, pharmacology and toxicology at the University of Arizona, and I'm a member of the Nonprescription Advisory Committee.

DR. CALLAHAN: Hi. I'm Leigh Callahan. I'm a epidemiologist from the University of North Carolina in Chapel Hill.

DR. HARRIS: I am Nigel Harris. I am Dean at Morehouse School of Medicine and a rheumatologist.

DR. KODA-KIMBLE: I'm Mary Ann Koda-Kimble, Chair of the Department of Clinical Pharmacy at UCSF, a member of the Nonprescription Drug Advisory panel.

DR. PUCINO: I'm Frank Pucino. I'm with the National Institutes of Health Pharmacy Department.

MS. REEDY: I'm Kathleen Reedy, Executive Secretary, Arthritis Advisory Committee.

DR. YOCUM: David Yocum, rheumatologist, University of Arizona.

DR. FERNANDEZ-MADRID: Felix Fernandez-Madrid, rheumatologist, Wayne State University.

DR. SIMON: Lee Simon, rheumatologist, Deaconess Medical Center in Boston.

DR. TILLEY: Barbara Tilley, biostatistician, Henry Ford Health System in Detroit, and I'm on the Arthritis Advisory Committee.

DR. LIANG: Matthew Liang, rheumatologist at Brigham and Women's Hospital, Boston.

MS. MALONE: Leona Malone, consumer

representative.

DR. MORELAND: Larry Moreland, rheumatologist, University of Alabama at Birmingham.

DR. MAX: Mitchell Max. I'm a neurologist at the Pain Research Clinic in the National Institute of Dental Research. I'm a consultant today.

DR. LASKA: I'm Gene Laska from the Institute of Psychiatric Research and from the New York University Department of Psychiatry. I'm a biostatistician and consultant this morning.

DR. BLEWITT: Good morning. I'm George Blewitt. I'm the industry liaison representative to the Nonprescription Drugs Advisory Committee.

CHAIRMAN PETRI: Thank you. Kathleen Reedy is now going to read our meeting statement.

MS. REEDY: Conflict of Interest Statement for the Arthritis Advisory Committee meeting on March 25, 1998. The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to prevent even the appearance of such at this meeting.

In accordance with 18 United States Code 208, general matters waivers have been granted to all committee participants who have interests in companies or organizations which could be affected by the

committee's discussion of pain claim structure for chronic and acute pain and onset of pain relief, including appropriate study design for prescription and nonprescription oral analgesics. A copy of these waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12-A30 Parklawn Building.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves for such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask, in the interest of fairness, that they address any current or previous financial involvement with any firm whose product they may wish to comment upon.

CHAIRMAN PETRI: Thank you, Kathleen.

Dr. Weintraub has a welcome and introductory statement.

DR. WEINTRAUB: Thank you very much, Michelle.

The problem of fast -- and the definition of fast onset and fast every aspect of drugs is one which is under intense scrutiny right now by the Food

and Drug Administration, particularly in the Center for Drugs, because everyone is jumping on it. Everyone wants to get a claim for fast, whether it's in the OTC or the Rx area, whether it's pulmonary part of the FDA or the neurologic part of the FDA or the OTC part of the FDA or the analgesic part of the FDA. Everyone wants to be fast.

We're sort of early in the process, however. These things have a way of moving through the agency, and we are a little bit ahead of the wave, although there is some interest from the people who watch our advertising for Rx drugs, prescription products, and there is now a movement in many parts of the Food and Drug Administration to deal with the issue of fast.

We started moving on it, because we felt the need, and it wasn't -- Dr. Hyde and Jim Kerner and others in the Division felt the need to deal with fast. What we're hoping for and what we're aiming for today is to get your input on the definition of fast, how we're going to apply the definition, what fast means to a variety of people.

Our hope is that we're going to get something out of our discussion today which will just be the beginning, and what we will try to do is join

with other forces in CDER, in the Center for Drug Evaluation and Research, and I hope bring our discussion of fast and everyone else's discussion of fast in line, and we're going to try and create some guidances and some thought pieces for the agency and for the industry as well.

I think the questions are good. They're a little hazy. They're not exactly to the point, because we are not sure exactly where the point is, but in any case, I know that from the agency that's what we would like. It is your discussion and your thinking on these points.

CHAIRMAN PETRI: Thank you. We have two registered speakers for the open public hearing, but others are welcome as well.

The first speaker is Dr. George Ehrlich from the University of Pennsylvania. Dr. Ehrlich.

DR. EHRLICH: Thank you, Dr. Petri, ladies and gentlemen.

When I saw that the -- in the Federal Register that the agenda this morning was going to consider fast relief, that hit a note with me, because in recent years I've headed the International Low Back Pain Initiative at the World Health Organization, and it's given me a different perspective on acute and

chronic pains.

Recently, when I was appointed Chairman of the Expert Advisory Panel on Chronic and General Diseases at WHO and a number of different aspects of treating pain came across my desk, it reverberated even more so. I was always reminded then that Dean Sidney Smith two centuries ago described his gout as "when I have the gout, I feel as if I'm walking on my eyeballs."

That's a definition of severe pain that no one would quarrel with if medical advice is sought, but it turns out that for much pain no learned intermediary is sought or, instead of standard medical case, people turn to alternative care such as acupuncture, chiropractic and neutraceuticals that are not under the purview of Food and Drug Administration in this country now, even more so in the world outside the United States.

Now when you have severe, acute pain, the definition of whether this pain requires intervention by a physician is usually decided by the patient on the basis of the prognosis that the patient sees in this pain. Many people never become patients. They remain consumers.

We as physicians tend to look on all

sufferers as patients, but they're not if they self-medicate. They are not. They have decided on their own that what they are experiencing is probably self-limited, probably self-treatable, probably not in the intervention and probably not serious; and that includes most headaches. That includes most rheumatic pains such as the ones that Ken Brandt talked about where his department proved that acetaminophen was an analgesic, as everyone knows it is; but that isn't really the full question.

If pain is prolonged or if it's certain types of pain, people then begin to worry about what it means, and it's for that reason that they consult learned intermediaries. Most go to -- for medications without learned intermediaries, and under those circumstances they want relief.

Now in chronic pain where you have repetitive dosing, clearly the onset of the first help is probably unimportant, as long as some help is received, but if you're self-medicating you want help reasonably soon.

The question is what are you looking for. Are you looking for total ablation for pain? That's probably unlikely for gouting pain. It's totally unlikely for toothaches from the result from

extractions. It certainly is likely for most headaches and so on, but most people are content if the pain comes down from a level of intolerability to a level where they can stand it and where it isn't interfering with the quality of life, and especially if they're not worried about what the pain portends.

So under those circumstances, I think fast is not a definition of time. One can argue about minutes, but I don't think that's relevant. People, since they buy these drugs themselves -- It's always reminded me of some years ago when I was still practicing and I saw a patient whose company made a beer that had a very, very good commercial, and one day they changed -- their agency changed the commercial.

He came in to see me, the President of the company, and I said, why did you get rid of that commercial? He said, well, everybody loved it, but it didn't sell our beer. I said, well, what was your sales curve? He said, well, originally it went up, but now it's back down where it was. I said, but that speaks for the quality of your beer, because anyone will try something the first time, but if they're not satisfied, they won't try it a second time. I think that's what the marketplace tells us.

Therefore, under those circumstances, the public defines what they want and what fast is; and if claims are made, I would assume that the FTC is on top of those claims. I'm not sure that necessarily the Food and Drug Administration should define what fast is or to what or where it is supposed to lead, whether it's supposed to lead to total ablation of pain, which is unlikely with most medications that you buy over-the-counter, or whether they're satisfied with the level that people can expect.

These are a few philosophical remarks which I hope you won't mind that I have taken your time for.

CHAIRMAN PETRI: Thank you. Does the committee have any questions for Dr. Ehrlich?

Our next speaker is William Soller, Nonprescription Drugs Manufacturing Association. Dr. Soller.

DR. SOLLER: Good morning, Dr. Petri, ladies and gentlemen. I'm Dr. Bill Soller, Senior Vice President, Director of Science and Technology for the Nonprescription Drug Manufacturer's Association. We are a 117-year-old trade organization representing the manufacturers and distributors of nonprescription medicines.

By sales, our members represent over 95 percent of the over-the-counter drug marketplace, and our members market all the major brand name and store brand products.

We're here, and I say we because these are comments from our internal analgesic task group which is membered by those companies manufacturing the major brand name and store brand products -- We're here to provide an OTC perspective on the claim fast and comparative claims.

We make a distinction between fast and faster, because often fast, we've found in our discussions, gets confused with the term faster. So I guess at the start, we would recommend that as you get to your discussions that you distinguish between the two. We prefer, and there are probably other terms for it, but to make that distinction by saying comparative claims, distinguishing them from fast.

A little bit of background: Onset -- we know when it happens, but it's hard to describe this from a scientific standpoint. For example, here a type of pain -- which of the at least eight types of OTC pain are we talking about? How does the intensity of initial pain affect the perception of onset, and how do the various analgesics, the single ingredients,

the combinations, differ mechanistically?

What are the implications of timing of dose for the initial pain and then for subsequent dosing intervals? Then, of course, individual variability on perception of pain, the ability to withstand pain, expectations of relief and the ability to distinguish between onset of first observable relief and complete relief? And this doesn't bring in other concurrent conditions that are non-pain conditions, as well as biopharmaceutics considerations in terms of a -20/+25 percent area under the curve and C-max rule for generic and brand names.

So this is a very complex issue, particularly in thinking on how to translate this into a rational regulatory context. And though complex, FDA has precedent in how to handle the claim fast on labeling.

FDA's OTC review defined broad reaching OTC policy on what FDA regulates in labeling, on the definition of effectiveness which is foundation to this policy, and how fast should be considered in OTC labeling; and while you're here to talk about the science of pain relief onset, it's important to consider the potential practical, regulatory application of this discussion.

So a little bit of background: I know the members of the Nonprescription Drug Advisory Committee are very familiar with the OTC review, but for those that haven't had a chance to consider this, this review started in 1972, and it covers the fast majority of OTCs on the marketplace and many OTC analgesics, aspirin, acetaminophen, by way of example.

It's a public review and comment process. It was set up to address the safety and effectiveness of all OTC ingredients that are not covered under New Drug Applications, a three-tiered process starting with a proposed monograph that is essentially a panel report very similar to this panel. It's published for review and comment, and then FDA issues a tentative final monograph, its overwrite of the panel report, going into another review and comment period to ultimately a final monograph.

For OTC analgesics, we are not yet at this final monograph stage. But my point here is that the OTC review has been the source of major OTC policies affecting how OTCs are marketed today.

So let's look at FDA's OTC policy on fast, and here there are four points that I want to make. The first is that FDA does not set standards for all OTC labeling.

Now stepping back for a moment, the Food, Drug and Cosmetic Act gives FDA the authority to set standards in labeling, on the one hand, and then to ensure that OTC labeling is truthful and not misleading. As FDA has set forth the standards, it has set also forth two principal objectives for the OTC review that relate to allowable ingredients and allowable labeling; but in stating this and in setting up these principles, FDA has said on more than one occasion through these published Federal Register documents that document the policy and the OTC review, that FDA has not determined that it's practical -- or FDA has determined that it is not practical in terms of time, resources and other considerations to set standards for all labeling found in drug products. These are OTC drug products.

Accordingly, OTC drug monographs regulate only labeling related in a significant way to the safe and effective use of the covered products by the layperson. I'll return to this, but again FDA set standards for labeling on statement of identity, on uses, on directions, on warnings, on listing of active and inactive ingredients now since 1997 in the new law, but there are other allowable claims, other claims that are on the label for which FDA does not

set standards per this policy.

Now as to the standard of effectiveness -- and this is a citation from the general provisions setting up the OTC review found in Code of Federal Regulations -- effectiveness means a reasonable expectation that in a significant proportion of the target population the pharmacological effect of the drug when used under adequate directions for use and warnings against unsafe use will provide clinically significant relief of the type claimed, and that the thesis to remember here is that it is a reasonable expectation, and it's a significant proportion of the population.

This definition -- Well, I should say this is not 100 percent here, and again focusing on reasonable expectation, because this definition is the basis for FDA's policy that all OTCs should work in a reasonable period of time. Here it's stated from one of several monographs that could be looked at.

In this case it's the monograph for dandruff, psoriasis and seborrheic dermatitis, but also you could look at antihistamines, decongestants, ingredients for oral discomfort where FDA states, as with all OTC drugs, they, whichever ones you're talking about, are expected to achieve their intended

results within a reasonable period of time.

I think this links well with the comments that you've heard from Dr. Ehrlich earlier. Nowhere has FDA in its OTC review making defined a reasonable period of time in quantitative terms.

So the fourth point on the policy is that FDA's policy hinges on whether the claim fast is related in a significant way to the safe and effective use by laypersons. Here, as FDA and companies have broached this policy over the last 20-25 years in the OTC review, FDA has repeatedly stated that the specific period of time within which, in this case, antihistamines achieve these results is not related in a significant way to the safe and effective use of the product.

So as a result, FDA has determined that the claim fast does not signal any property that is important to safe and effective use of OTC drugs. Therefore, it's not within the scope of the OTC review. That's a term of art, regulatory art, but what that means is it's not a part of required labeling, remembering that you can have nonrequired labeling as long as it's truthful and not misleading elsewhere.

So that, even if a claim is outside the

review, it still must be truthful and not misleading under the FDC Act, and there's one occasion that I'm familiar with in the many documents that cover the OTC review, and that's the topical antifungal where claims on fast were made, but the labeling states that you need to take this product for curing athlete's foot for two to four weeks before you get a full effect and, therefore, that claim was misleading. FDA made a statement, and essentially that claim is not made for those category of products.

So in applying FDA's policy, there are two basis principles. Does the claim significantly affect safe and effective use of the product by the consumer, and is the claim misleading, all in the context that OTCs are expected to achieve their intended results in a reasonable period of time, and that effectiveness is a reasonable expectation of relief.

So here we have examples of OTC ingredients where FDA has placed fast outside the scope of required labeling for the nasal decongestants, for congestion, stuffy nose and the antihistamines, runny nose, sneezing, anti-dandruff, anti-psoriasis, anti-seb dermatitis, for itching.

We would maintain that for OTC internal analgesics, as we look at headache, menstrual aches,

aches and pains, that they fall within the same conceptual realm and, therefore, should not be a part of required labeling but, obviously, allowed the claim fast outside the scope of that OTC review, and I would just ask that you recall some of the comments from Dr. Ehrlich that fit this policy very well.

Dr. Ehrlich also mentioned the FTC. This is a matter of administrative law as well as implementing regulations, but this is an interesting quote from the OTC review of the topical antifungal TFM, tentative final monograph, where the agency, FDA, agrees with a reply comment from a company that FTC has the primary responsibility for regulating OTC drug advertising and recommends that concerns about truthfulness of advertising claims or implications be referred to the FTC.

The FTC has an established structure for addressing claims not required in labeling, and my point here is that the claim fast is not without regulatory oversight.

So in summary, fast as a claim for internal analgesics should remain outside the scope of the FTC review. By that, we mean not be in required labeling. It does not significantly affect safe and effective use of an OTC analgesic. They are intended

to work in a reasonable period of time, and remembering that analgesic effectiveness is defined as a reasonable expectation of pain relief.

We believe that that is conveyed by the statement, fast pain relief. Fast is a qualitative term, should not be defined quantitatively in labeling.

Finally, unlike fast, faster is a comparative claim. We think that should be handled on a data driven, case by case basis. We also think it's very difficult, and we don't envy you the job of trying to generalize the scope and nature of a comparative analgesic claim in the absence of ingredient specific data.

In any case, we do not support rigid numerical criteria for faster, given the wide variety of factors that affect onset of pain that I went into earlier, and then the difficulty of taking that complexity of onset of claim and trying to translate that into a practical regulatory context.

I thank you for your time.

CHAIRMAN PETRI: Thank you, Dr. Soller. I wonder if I might ask Dr. Weintraub is he could respond to the committee about what is outside or inside the regulation.

DR. WEINTRAUB: The main point we want you to consider today is the issue of how we're going to define fast and how we're going to study it.

This is a critical question, whether it's inside the review or outside the OTC review, whether it's inside analgesics or outside analgesics, if you will. It's a cross-cutting concept. That's the point I was trying to make before.

So while Dr. Soller's comments are very helpful and very important, they really are one person's interpretation of the regulations. As you saw, internal analgesics were not in the same category. He had them in a box underneath.

We are going to -- I think the committee's job, in a sense, is to do your thinking without being encumbered by regulations. We'll worry about the regulations. Dr. Soller will worry about the regulations, but what we're asking for from the committee is a free wheeling discussion of the issue of fast, and we will take care of the rest.

CHAIRMAN PETRI: Thank you. Are there other participants for the open public hearing? If so, if you could please go to the microphone and identify yourself. Seeing none, we'll move on.

Today there is an obvious division between

the morning and the afternoon. The morning session is going to be on fast onset of pain relief for prescription and nonprescription oral analgesics, and I'll turn this over to Dr. Weintraub.

DR. WEINTRAUB: Dr. Laska, do you have a presentation? Actually, I would prefer that Dr. Laska present his stuff, and also Dr. Max's presentations as well.

DR. LASKA: This talk actually works either upside down or backwards.

Good morning, ladies and gentlemen. The issue of characterizing onset, both its measurement issues and the analysis of the resulting data, is indeed a vexing one and an important one in many areas.

One of the areas I've also done some work in, in the psychiatric field, deals with pain presence where the issue of the rapidity of effectiveness in treatment can make a difference in a life or death situation. So despite the regulatory issues, the clinical and scientific issues remain of rather great magnitude.

In the thinking that went into the notions of characterizing onset, I want to acknowledge my colleagues, Carole Siegel and Al Sunshine, who have

been intimate discussants about what makes sense and what doesn't, and their contributions are reflected in these slides.

First, what's, in my view, not a good thing to do: That is, it's not a good idea to base estimates of the onset of effectiveness of the treatment in terms of mean effects that are collected at fixed time points over time.

You will recall that the conditional analgesic trial is comprised of a bunch of observation points in time, usually 15 minutes, 30 minutes, an hour and a hour thereafter, and patients are asked about the effect level, how much relief they've gotten at each of those time points.

These two hypothetical curves, treatment A and B, at the 30 minute time point you can see that the mean relief score of treatment B is higher than the mean relief score of treatment A, and yet if E defines some onset event, then the treatment A has an earlier onset than treatment B. So at least it's theoretically possible that one can draw the wrong inference by looking at, in effect, sizes at fixed time points.

Instead, beginning in about 1991 or '92, a clinical paradigm was adopted widely in the

analgesic research clinical trials world which was based on the use of a stopwatch. Patients were given a stopwatch and asked to click it at the time they experienced some kind of clinical event that needs to be defined.

There are at least two that have been used fairly widely. One is perceptible relief, and the other meaningful relief. So on a relief scale from zero to 100, a patient is asked to keep in mind the concept of, let's say, meaningful relief, to click the watch when that occurs.

No definition, although some verbal characterizations of what meaningful relief is about, are given. So we cannot say meaningful relief will occur when you have received, let's say, 30 percent improvement over baseline.

Similarly, perceptible relief, not easily defined, but the notion being when some kind of an effect is felt, please click the stopwatch. In an innovation introduced by Rudy Widmark, two stopwatches are sometimes given. The patient is asked to click the watch when perceptible relief occurs, and then click it again a second time when meaningful relief has occurred.

In the figure you see that the

intersection of the level of pain or relief, let's say perceptible relief -- the intersection point with the effect curve is the time at which perceptible relief occurs or the time to meaningful relief. Those two concepts, the times, are the basis for analysis of where onset is all about.

Clearly, a third concept, complete relief, mentioned by previous speakers, plays a whole here, too, and it could be important to know when the time to complete relief occurs, if indeed there is complete relief.

So the data that is collected in a clinical trial where estimating onset is concerned -- the data consists of a bunch of time points at which these events have occurred, and for some patients, of course, the event has not occurred.

What are the parameters that can be used to characterize this onset? One important one that is debatable as to whether it's a measurable onset but which enters, clearly, conceptually is the probability of having onset. Clearly, in clinical trials of analgesics, as the severity of the pain increases, the probability of having onset decreases.

The issue of what is the time to onset for those patients who have onset is a clear and

understandable characterization of the onset curve.

So s(t) -- please don't get tied up in the notation. s(t) is just simply the probability distribution of time to onset among those individuals who do get onset.

The third parameter, if you will, of characterizing onset is the entire distribution. It's the total set of times in which patients get onset. That's denoted by h(t) at the bottom. That describes the same thing that s(t) describes, the times to onset, plus the times at which patients no longer are in the trial, the ones who were censored because of trial end or because of other events.

The first goal is to estimate these parameters so that one can report both to clinicians and patients what those probabilities are and what those time distributions are.

Moving to the comparative claim issue, the question of whether one drug is faster than another really is a little more complex than the simple English language statement that underpins the question. One issue is are the probabilities of onset the same across treatments?

Clearly, these probabilities will depend on the nature of the pain and the severity and perhaps

other issues. So the complexities that Dr. Soller mentioned obtain here as well, but within a single degree of pain relief and within a single etiology the question of whether the probability of onset is the same for all treatments is clear.

A second issue, the conditional question: For those patients who do receive onset, what is the distribution function of time to onset, and are they equal across treatments? These two hypotheses and a third, the unconditional one, taking all of the data into account, represent the candidates that people have looked at in the field, that people have used to answer the question about the comparative rapidity of onset.

The difficult issues on choosing on which measures to use, perceptible pain, meaningful relief and so on, are mirrored in the difficulties that have -- that the data collection challenge brings out, and that is the two -- the center box in the middle of this foil, and that is patients don't always stay to the end.

They drop out of the trial because of insufficient relief or for other reasons, and for those people it's difficult to know whether they would have gotten onset if they had stayed in the trial or

if they would have been a nonresponder, had they lasted until the end of the pharmacologically meaningful time that onset could have possibly occurred.

So any statistical analysis that is derived and used on these data has to take this into account.

That takes us to the traditional ways in which censored observation analyses take place, something that derives from early work by Kaplan and Meier using estimates of the survival distribution, which here means the probability of onset. In the upper foil this hypothetical Kaplan-Meier estimate of the time to onset shows that half the patients receive onset by about 140 minutes, two hours and some minutes. Roughly 47 percent of the patients ever go on to get onset.

So in this top estimate of the onset curve, we have a characterization of the onset time which takes into account all subjects, including those who never get onset.

A second way to think about it, the conditional way I described earlier, is described in the bottom curve, bottom Kaplan-Meier curve. Here it's the same hypothetical data that's in the top

curve, but the analysis is restricted only to those individuals who on to get onset.

Here the median time to onset, the time corresponding to that red line, is about 50 minutes. So the data is the same, but the interpretation changes. Among those individuals who get onset, the onset time, the median time to onset, is about 50 minutes. In the whole population median onset time is around 140 minutes, and the difference in those two is conceptually clear, but needs to be taken into account when claims are presented or made.

Why is this important from a clinical point of view? There are many, many reasons, obviously. Here is one simple illustration of again a hypothetical curve which describes as time goes on the conditional probability of getting onset, given the patient hasn't had it yet.

So down at the baseline period, there's some probability that the patient won't get onset, represented by 1 - b. Let's say it's 80 percent, probability of .8, that the patient will not get onset. So it's a drug that mostly works.

As time goes on, that probability of not getting onset increases, and it approaches about half at about an hour and a half in this hypothetical

curve. So it would make sense that, as time gets closer and closer, let's say, to two hours, it would be a time to recognize that the chance of having no onset is very high. Maybe it's time to consider remedication, increasing the dose or some other strategy.

These kinds of treatment curves, these kinds of guidelines for treatment, come out of knowledge about what the distribution of onset time is and the chance of having onset, and whether or not they apply to regulatory issues is not as relative as the potential benefits that knowing these parameter values could have.

Thank you.

DR. WEINTRAUB: Gene, if you could wait at the podium maybe for some questions or comments.

I want to make a similar statement to the one I made yesterday. I hope the FDA representatives will jump in here and ask questions as well as the committee, because this is -- As I said, this is a different field for many of us. We're trying to learn, and so some people may have questions.

CHAIRMAN PETRI: I'd like to echo that we welcome audience participation as well. Dr. Liang.

DR. LIANG: Just a couple of questions.

Is it known or can you give us any information on the trajectory of response curves for placebos in analgesic trials?

DR. LASKA: Yes. The issue of placebo is a fascinating one, both here and in any present trials where the same kind of analyses have -- have done the same kinds of analyses. Placebo response rates, generally speaking, not surprisingly, are very much lower. That is, the probability of getting onset is very much lower from placebo.

That turns out not to be a difficult thing to pick up. But conditional on getting onset, placebo response rates are very rapid. It should be no surprise, therefore, that a drug will not show itself to be faster than placebo, given that you only look at those patients who have gotten onset, the conditional time to the effect.

When the unconditional analysis is done, placebo looks terrible, because of all those people who never get a response time. So median response time may be at the end of the trial, but for those patients who get response very rapidly.

Even though it's not quite relevant to the onset story, interestingly, there have been people who have argued that the onset times of most drugs that

work are roughly the same, and what appears to be differences in onset time are really differences in the probability of getting onset. That's been noticed in psychiatry trials.

DR. LIANG: Could I just do another one?

CHAIRMAN PETRI: Yes.

DR. LIANG: This is somewhat related, and I know this is probably not applicable to OTCs, but is the rate of onset measured at what you want to relate it to the likelihood of habituation or addiction?

DR. LASKA: I don't have information on that question.

DR. LIANG: Then, finally, it makes a difference, I think, whether the rater is naive to the analgesic or has seen it again in terms of, you know, the second and the third points, in terms of their expectations. Is that changed by -- Has that been studied?

DR. LASKA: In a sense, it's been studied. Rudy Widmark has made a considerable contribution by arguing that the value of that first stopwatch for perceptible pain clicking is that it is a signal to the patient, pay attention, as is things like the size of the watch. Pay attention; you're starting to get

relief now.

For the second click, there is some kind of a confirmation that the first click was real. Pain was really starting to go away. Also, it may make the second click more valuable, because it has highlighted this expectation phenomenon.

CHAIRMAN PETRI: Dr. Simon?

DR. SIMON: I was wondering if you could help me. Does chronic pain have the same common response than acute pain?

DR. LASKA: I have not looked at studies in which that issue has arisen. So I can't help you.

DR. SIMON: But might you speculate that, given the fact that most of us who treat patients with arthritis who have pain have a remarkably significant and sustainable placebo response rate in the sensation of pain or at least what they report as pain -- I was wondering if you could speculate as to what perhaps the differences might be if there isn't such a sustainable placebo response rate in the onset of relief from acute pain?

DR. LASKA: I suppose I could speculate, but I think I'd rather let you.

DR. SIMON: Gee, thanks.

DR. MAX: Most of our work at NIDR is

studying chronic pain, and we've reviewed the literature, and there just hasn't been the kind of methodological attention to onset that's been applied to these acute surgical studies. I mean, theoretically, Gene pointed out to me that, if you're doing a six week study of neuropathic pain or arthritis, you could apply the same methodology; but I don't know if anybody has done it.

CHAIRMAN PETRI: You might have to have a stopwatch that went for days, though. I have a question.

You commented that one of the most important questions for consumers is when should a patient take a different drug, but in our background reading it was pointed out that the drug levels may be varying quite a lot between individuals.

So perhaps the question should be when should the patient take a second dose of the same drug?

DR. LASKA: Absolutely. That was one of the intentions of that kind of analysis, and there is data that supports this notion about poor blood levels tends to imply poor response rates. So it may be true that, if you had waited, the blood levels would have gotten high enough. The response would have happened

whether or not you take the second drug.

Remember, these kinds of curves are population based curves. They're not for individuals, and they are based on only clinical data, not laboratory values. So if that were to be a serious -- and it is in some corners serious research, the connection of serum levels to event effect levels -- one could answer the question with more clarity and certainty.

From strictly the clinical data, the response data, these curves tell you what's going on with regard to the likelihood of getting an effect if you haven't had one until now, and I think they are guidance that are useful to have.

CHAIRMAN PETRI: But in terms of a consumer, shouldn't the consumer know if there's great variability in drug levels with a product?

DR. LASKA: I think you have to ask Michael that.

CHAIRMAN PETRI: Dr. Liang?

DR. LASKA: I'm sorry. Ken.

CHAIRMAN PETRI: Oh, I'm sorry. Dr. Weintraub, would you like to -- Dr. Brandt?

DR. BRANDT: Another question related to the placebo response, and you mentioned the rapidity

of the placebo response: Is there any relation between the rapidity of onset of the placebo response and the duration of the placebo response?

DR. LASKA: I don't know. That's a very interesting question. The duration -- I'll give you my subjective response -- in the studies I've looked at is very short, but whether or not it's related to how fast the individual patient gets onset, I'm not sure; but as a general principle it's very short, particularly in the more severe pain.

CHAIRMAN PETRI: Dr. Koda-Kimble.

DR. KODA-KIMBLE: How does the natural history of pain fit into this model? I mean, if you have a pain that is self-limiting, how do you work that in?

DR. LASKA: The traditional analyses in clinical trials are done on, for example, dental pain where, in a sense, the pain is getting worse after the anesthetic wears off, and perhaps in other pains it's going the other direction, the further away you are from the insult. But these methods have nothing to do with onset. They have to do with the general -- these questions that you are raising have to do with the general question of how you do clinical trials in analgesics.

For analgesics, we essentially ignore the natural history of the pain. There is some event. Treatment is given, and if the level of severity of the pain is high enough to require intervention and then we follow that patient. So there is really no difference in the onset story than there is for any other effect calculation.

CHAIRMAN PETRI: Dr. Liang?

DR. LIANG: Any data on intra-rater -- inter-rater reliability of this stopwatch?

DR. LASKA: Well, the good news here is that the patient is the rater. So the answer is, no, we don't have any inter-rater reliability.

DR. LIANG: I'm sorry?

DR. LASKA: Well, it's the patient who is doing the rating.

DR. LIANG: I understand, but suppose you had the same noxious stimulus, same medicine, and you had repeated it a week later. Would they --

CHAIRMAN PETRI: Dr. Liang is going to take out a second tooth for reproducibility.

DR. LASKA: Yes. There are clinical trials, as you know, that are done where there's a crossover one week. For one treatment, the patient --

DR. LIANG: Yes, but I 'm looking for a

number --

DR. LASKA: Yes, I understand. There is no information.

DR. LIANG: Oh, that's striking.

DR. LASKA: Well, you know, there's other things. There is evidence that these methods work, and the evidence is based on doses that show increasing onset time and treatment study appear to be faster than others, which are consistent with pharmacokinetic considerations.

So from the big picture, you can separate drugs and you can show the "dose response times." Whether or not patients are able to replicate this phenomenon would be a question even if you did that study, for the simple reason pain varies so much, the setting varies and a whole host of other things.

I'm not sure what -- It's certainly worth doing, if someone were to sponsor it, but it isn't a high priority from us or the pharmaceutical companies.

CHAIRMAN PETRI: Dr. Fernandez-Madrid.

DR. FERNANDEZ-MADRID: To follow up the same question, how reproducible are the first click and the second click in the same patients on different occasions?

DR. LASKA: I've only looked at a few

trials with this data. So I really can't give you a learned comment, but from discussions with Rudy Widmark, there are patients who will click within seconds. The first click is followed immediately by the second, which kind of maybe implies that the patients were asleep at an earlier time point or weren't paying attention.

There are other trials where it never -- the second click never occurs. So that may be that the first click was an accident. So consistency of this kind is highly variable. It depends on the trial and the severity of the drugs -- or the effectiveness of the drugs, severity of the pain and so on.

I assume that was your question.

CHAIRMAN PETRI: Could Dr. Widmark also respond? Dr. Widmark? Would you mind coming to the microphone.

DR. WIDMARK: We did not have data that would reveal the reproducibility in the same patient to the same drug.

There are models out there where it could be done, like dysmenorrhea trials where the patient takes the same drug at the same time period several times. So it could be done, but we have no data at this time.

DR. LASKA: I would also like to say that there are many who feel that a perceptible relief is not a very important measure, because it really only signals some event has started. Now it's time for this drug to start working.

What's important, some say, is the time that the patient says now I'm really getting relief. This can be characterized as meaningful and significant. From one of Dr. Soller's slides, the word significant was used.

The concept here on how this thing is working tends to have more -- many clinicians feel, more clinical sense than when it's just this little perception occurs. So maybe the point about how these two are related is not that critical.

CHAIRMAN PETRI: Dr. Tilley.

DR. TILLEY: I'm a little concerned then, given what you showed us, first of all, those two curves that showed the difference in time to onset, whether you put in the people that didn't respond at all and the curves where you had just the people that did have onset.

I guess I'm concerned talking about fast than by itself. I mean, it seems to me, given what you said about placebo, that if we just talk about

onset time alone, we could be saying a lot of drugs are faster when they're like placebo.

DR. LASKA: Right.

DR. TILLEY: So I guess what I'm wondering about is, you know, the advantage to the old fashioned way was that you combined those two pieces of information together. The disadvantage was you didn't know in the patients who actually did respond when that onset time was.

So I guess I'd just like your thoughts about this kind of, you know, problem here, because I would hate to see fast, you know, in your approach reported without the accompanying percentage of patients that had onset.

DR. LASKA: Well, I strongly believe that, first, because Barbara is a statistician. The analysis isn't really just confined to patients who respond. The censored patients come into it as well. So it's a more complicated statistical process -- condition.

DR. TILLEY: But still, could you envision a situation where the placebo would still look better and have a small number of responders?

DR. LASKA: No, I don't think that's likely to happen, but I think the other is liable to

happen. That is, a patient population that does not respond and there's a large fraction who don't respond, but of those that do, you get fast response.

You can make that look like it's a slow responding drug by looking at the entire analysis; that is, without conditioning on the responders. So you can be badly misled about what's going on. That is a possibility.

CHAIRMAN PETRI: The back microphone.

MEMBER OF THE AUDIENCE: Good morning. My name is Dr. Nick Holford. I'm a visiting professor of clinical pharmacology at the Center for Drug Development Science, Georgetown University.

My comments relate to Dr. Laska's talk and to the comments that the panel have made so far. I believe that the concept of the probability of onset is important, and I think you've very correctly pointed out the problem of censoring and how that occurs. However, your remarks and those of the panel have suggested that you've incompletely described the components that lead to pain relief.

They've been touched on, but I'll just emphasize what I see them to be. First of all, the progress of the disease, the pain course, time course itself. I think that has to be considered when

interpreting any pain relief.

Secondly, there is the response to the placebo. You've mentioned that, but I believe you said you essentially ignored it, although not completely, in your formal analysis.

Thirdly, there is the drug itself, and there's a vast science about pharmacokinetics and pharmacodynamics that allows the science of the drug to be put into that as well.

So there are three components to the model, the disease, the placebo and the drug itself. I believe that in this situation where you're trying to resolve a small signal in the presence of a lot of noise, and trying to understand the basis for that signal, that those three components have to be considered simultaneously.

I believe, Dr. Laska, you're aware of Scheiner's approaches to modeling just these kinds of problems, and indeed the model that he uses includes those three components. I would ask the committee to be aware of that, if they're not already, and that there are approaches that do bring science of what we know about drugs and how they work into understanding these problems, and not simply treating it as a black box in which the patient clicks a stopwatch, and

trying to interpret basically everything from the stopwatch clicks.

CHAIRMAN PETRI: May I ask you to elaborate on this, because the committee is not aware of these other models. Can you tell us why it would be different, better, what the limitations might be, of another model?

MEMBER OF THE AUDIENCE: Well, it's certainly complex. They are relatively complex models statistically and, I would say, structurally, in terms of their pharmacokinetic/dynamic components and the placebo response and disease component responses, that the methodology involves nonlinear regression, mixed effect modeling, and the use of these probability distributions in that analysis. So --

CHAIRMAN PETRI: Would it be based on the same sort of stopwatch technique? Is what happens to the patient the same, and it's just the statistical modeling that's different?

MEMBER OF THE AUDIENCE: Well, let me make it quite clear. There's a big difference in my mind between an analysis technique and a method of measurement. Stopwatch is a method of measurement, and as are other measures of pain relief or the change from baseline is a pain score.

So there's a method of measurement. What I'm talking about, and I believe what Dr. Laska is talking about, are methods of analysis of those measurements, and the methods I'm referring to can be applied to both kinds of measurements, whether that be time to some event or whether that be some score of pain relief or pain score at some point in time.

CHAIRMAN PETRI: I wonder if someone could help me, and define this different form of analysis. Dr. Laska, could you --

DR. LASKA: Lou Scheiner has written extensively on this topic, and just recently in a statistical journal, Journal of the American Statistical Association, describing these models very, very technically. They are an advance, and they are a major contribution, but one should not lose sight of the issue of the simplicity of looking at clinical outcome data and analyzing it without the use of more elaborate models, which have a purpose, which are useful but which are addressing sometimes other issues.

In particular, Lou has a very, very carefully constructed model for linking blood levels and effect size to try and determine what other biological factors go into making that outcome occur,

and then describing the parameters that drive the system, trying to identify which are the important ones and when events occur.

Now here we're into a very different setting, one that involves clinical care where the availability of blood level and fixed observation points does not come into play.

Also, Dr. Scheiner has not really focused attention on the onset story as much as he has on effect size, and I'm sure his models can be adopted to make use of those, and it would be a welcome addition to the scientific literature. I think, however, from the perspective of looking at how to characterize the events, simplicity is called for.

The complexity of the clinical setting and whether or not something compares to placebo in one direction or another has to be considered, but if we throw up our hands and say it's too complex to look at, we get nowhere. If one stays within some kind of severity level and some disease entities that are delimited, I think these generalizations are valid.

CHAIRMAN PETRI: Dr. Simon?

DR. SIMON: I realize you may not be able to answer this, but perhaps you can shed some light so that I can begin to grapple with it.

I've always been challenged by trying to figure out how OTC analgesics work, what their biological mechanism of action. I was wondering if you had looked at the effect of opiates as an analgesic in this particular model and determined a different response system than you might find with the OTCs.

As has been suggested, is it more complex than just blood level and availability, but is it also the actual biological mechanism of action that defines this kind of modeling in this manner?

DR. LASKA: Regrettably, I can't answer, but I can tell you that in Dr. Sunshine's early experience with using the stopwatch after we had proposed it, it was with a narcotic. The question was are you getting -- or some version of -- are you beginning to feel any pain relief. Before the nurse observer walked out of the room, the patient was raising her hand.

So onset times, certainly, are different when the opioids are studied. Whether the biological mechanism is different is not easy to tell.

CHAIRMAN PETRI: In our reading there was also the suggestion that, if the analgesic is also a sedative, it might affect the accuracy of the

stopwatch technique. Is that an issue?

DR. LASKA: There is no question that you have other phenomenon come into play. In the antidepressant world, sedation makes the drug look like it's an antidepressant when it maybe just takes the edge off. So you've got to look at what it is you're trying to measure, and other effects can come into play.

CHAIRMAN PETRI: If I could ask a question about how we're defining the different periods. We have onset and meaningful relief. Then there was complete response. I was trying to put myself in the position of a patient with a stopwatch.

How does the patient know when there's complete relief, because it might get better. Doesn't the patient know when the relief is wearing off, and wouldn't that be a better way if you're going to have a three-stopwatch?

DR. LASKA: Right. We have not -- I don't believe anybody has looked at a stopwatch measure of complete relief. The second stopwatch in most people's use of this are for duration, measures of offset. When does the patient feel -- is no longer getting adequate relief from the treatment, and the watch is clicked.

Then there's a whole 'nother set of issues and analysis saying how can you measure duration unless you've had onset. That's a topic for another day, but in my judgment, that's correct. One should look at some measure of early time phenomenon, probably meaningful relief, and some measure of no longer working, and those two characterize what's going on

CHAIRMAN PETRI: Dr. Simon.

DR. SIMON: Just to extend one more thing about the issue of sedative or the sedative effects. If you -- In a pain model like this, and if you took a drug that would be considered a muscle relaxant or in some situations is an antidepressant but is used as a pain reliever in ankylosing spondylitis or an acute pain -- muscle pain syndromes, do they give you the same kind of dose response response curves?

DR. LASKA: No experience of those.

CHAIRMAN PETRI: Dr. Kent Johnson and then Dr. Fernandez-Madrid.

MEMBER OF THE AUDIENCE: One quick question of information, and then I have a question for both you and the fellow from Georgetown.

Is the most persuasive, clean model for pain dental extractions, in your mind?

DR. LASKA: It's a clean one.

MEMBER OF THE AUDIENCE: And those are always done in the setting of an anesthetic that's wearing off?

CHAIRMAN PETRI: Your answers will have to be at the microphone. Please, let's switch back on.

DR. LASKA: Yes, to both those questions.

MEMBER OF THE AUDIENCE: Well, that strikes me as an obvious sort of confounder. That, obviously -- I'm sure it is addressed, but may still not be adequately be teased out here. But it strikes me that what you have is a theory -- I mean, you have a model, and it's a model that can be proposed as a theory, and one would hope that -- and the same is clearly true for Scheiner's work.

Then in the setting of sequential randomized trials and drug development or something like that, you would do a study, and you -- and the study fails, but you generate another hypothesis. You then test that hypothesis.

When I've talked to the modeling people in the Scheiner group, that always strikes me as the challenge, you know. If this approach is so effective, predict what would be the best trial, and then do the trial, and the trial -- if the trial is

dramatically successful, then you've sort of corroborated your model.

I think the same is probably true here. I don't know if there are scenarios where, from your perceptions of these things, you could predict that, you know, phenomenon X would occur and then actually test it. If it does, then you've got support, and otherwise you don't.

CHAIRMAN PETRI: If I could ask a follow-up question about these other modeling techniques. I assume they just include --

DR. LASKA: Can I respond to this gentleman?

CHAIRMAN PETRI: Yes, please.

DR. LASKA: I did mention earlier -- By the way, the word cleanest trial doesn't necessarily mean best or one without difficulty, but I did mention before that one sees dose response, higher probabilities of onset for higher doses, earlier onset times for higher doses. Also, one sees differences among treatments where one would expect to have early onset times because blood levels occur earlier.

These are corroborating, supportive validation that these models work to distinguish and to give valid primers.

CHAIRMAN PETRI: I wanted to ask again about Dr. Scheiner's work, because I'm not aware of it. It includes other confounding variables in the statistical analyses, such as sex, race, age, education?

DR. LASKA: Almost all of these kinds of models have the ability to include whatever you want, and one of the dangers of the Scheiner type model is you include too much. You put in so many parameters that you have the potential for overfitting the data, and every model will fit the data.

Lou is a very fine scientist, and he is acutely aware of these issues, but that potential for including those kinds of effects are surely present, and they are here, too. I just gave the simple version.

CHAIRMAN PETRI: Dr. Fernandez-Madrid.

DR. FERNANDEZ-MADRID: I have a concern about the validity of the measurements, and I would like to hear a more critical discussion of the validity of the measurement than I am able to make.

When we do an experiment and the experiment is done by an external observer, we look at the reproducibility. We look at the interpreter variability, a variety of things to validate the

method.

In this case, the observation is made by the patient, and the patient is influenced by many factors, by expectations, by sedation, by medications, by variability in the disease and so forth. So I really would like to see how reproducible are these two clicks, because this has bearing on the data.

If the data that you put in the model is fuzzy -- it is not a point, but it is a zone -- then the results would be different.

DR. LASKA: I'm sure you'll hear as the morning wears on clinicians give you a better response than I'm able to give, but I would say that whatever your concerns are for this method, they should be less than the concerns for the general traditional clinical trial in analgesics where the patient is asked, tell me if your pain is mild, moderate or severe.

Here, you have a quantitative understanding of what the measure is. It's a time to an event. We all understand that this event took place in 20 minutes or 40 minutes or two hours, but the other one where we assign a 2 to the value of moderate, here we start getting into a little bit of things to worry about in terms of reproducibility and meaningfulness.

I think here you're on more solid ground.

CHAIRMAN PETRI: Question from the audience, and always please identify yourself.

MEMBER OF THE AUDIENCE: Yes. I'm Paul Desjardins. I'm the Associate Dean at University of Medicine and Dentistry, and I'm currently the head of the Pain and Analgesia Section of the ASCPT, Society of Clinical Pharmacology and Therapeutics.

The gauntlet was thrown to the scientists to participate at the ASCPT and to numerous investigators about six years ago to determine whether we could come up with a more valid, more reproducible and quantitative measures of assessing onset of analgesia.

What you are seeing today is an evolution. The first set of data of trials which has really been conducted in the past three or four years has shed some light. These are questions which can be answered.

there are numerous other questions about whether the methods are generalizable across all types of pain. There is a fairly large body of data, Michael, I believe, which you receive at FDA, especially in dental pain, but not only in dental pain, in headache, in dysmenorrhea.

One of the things which I think that the work has done in the fast four or five years, Gene, is that we've standardized how we've asked these questions, and we do have data on the reproducibility and even better data on the validity when we've gone back and asked patients who confident were they about pressing those stopwatches.

They give us, on a zero to ten scale, numbers of seven to eight in terms of I was fairly certain that I had pain relief; and on the meaningful relief scale, they're really at the other end of the scale. They talk about 80 and 90 percent certainty that they really had relief when they stopped that second stopwatch.

These -- Again, it is a very broad set of questions, and I'm confident from the data that I have seen that these are questions which can be answered with data, not by speculation, not by guesses as to which is a single best measure, but by going out and testing hypotheses.

The agency has provided some guidelines to drug development people who have wished to have some of those onset claims, and they've asked for specific data. The difficulty and one of the challenges for some of us as scientists is that we don't see the

broad data from all the investigators.

You have an interesting opportunity at the agency which many of us as the scientists who do the study do not have, but again I would argue that we do have a panel as well at the ASCPT, the Analgesic Guidelines Committee, who has in the past been willing to help develop specific guidelines to assist the agency in making some of its decision.

Again I would offer the assistance of the Analgesic Guidelines Committee, of which Al Sunshine is the Chair, in assisting the committee in drawing some of these conclusions, based on some of the data which is available. Thank you.

CHAIRMAN PETRI: Dr. Max.

DR. MAX: I'd like to make a few comments. First of all, I've looked at several dozen studies in dental pain, other surgical pain, and headache, several other conditions. Generally, the one aspect of validity is the outcomes with the stopwatch for meaningful relief agrees with the results of the means except that it gets directly at individual responses.

So if you're interested in seeing what proportion of patients will respond or putting on the label how soon you should take medicine, the stopwatch technique gets at this directly, and the means can't

do it.

I agree with Paul that there has not been a large meta analysis looking at -- or a large study of the validity, and many, many studies of that could be done.

Secondly point: There's a publication in the binder that -- where he found in one study that the perceptible relief is much less discriminating between drug and placebo than meaningful relief. I think that's the general -- You know, just about every study that I've looked at and most of the people I know have looked at has that result.

I mean, it's easy to get perceptible relief with placebo, but as you raise the bar, you get a greater separation between drug and placebo. So perhaps in conditions that are hard to relieve and get complete relief, it becomes harder, but perceptible isn't so good.

Third comment is: How about the word meaningful relief? I'm in a group with psychologists who have looked at pain words, and they get a little uneasy with the word meaningful, because the tradition is to look at pain intensity and have a whole set of words describing intensity and pain affect and, you know, have words describing how unpleasant or

miserable.

Meaningful comes from a non-psychologist, and it doesn't fit into that framework. So that -- You know, a lot of people don't like it for that. I prefer to use words -- We're already asking patients is relief no relief, slight relief, minor relief or some relief, a lot of relief or complete relief, and you want to use the same words you're using to activate a stopwatch and give the patient less of a burden and have a much greater amount of data to support it.

So I have a preference for that. However, you know, meaningful has worked. Now I don't think it's a huge issue whether you use meaningful or pain half gone or some relief for the stopwatch.

Then the point comes, what are you going to make -- what about claims of fast? I think it's very tricky if you just say define a drug as fast or not fast. There are going to be a lot of people screaming, because they will think it's unfair if they just miss it or they get it.

One concern is that models vary. So pain -- the time of onset of pain relief can vary tremendously with placebo response or how fast the drug gets in, the patient's fed or fasted state, the

nature of the procedure.

For that, oral surgery -- If the FDA wanted to establish a baseline, a gold standard, a model, oral surgery has the advantage that -- Steve Cooper wrote a chapter in 1991 showing that the oral surgery model has the least placebo response of the commonly used surgical models.

It's done so often that people technically can get it to work similarly. So the results are more likely to be comparable, and we could figure out how to make it comparable.

You could say the conditions should be that they are fasted with a certain amount of dental trauma, etcetera, and you can't get that standardization with other models. So I think it might be wise, if one wanted to set up criteria, to pick a model like oral surgery with certain conditions, say that you need two studies to do it, and you need a comparative; because even within the oral surgery model, the placebo response can vary sometimes.

If you just take onset within 30 minutes to be fast, that will vary from study to study. I think you need a standard such as if you wanted to take the Nuprin or some standard for each drug that

you had to compare it against, and you had it be faster than a standard by ten minutes or some arbitrary thing that you think is meaningful. That would be the way to do it.

Finally, I would suggest that the consumers can absorb actual numbers. So if you actually put the data -- say this is 15 minutes after, 20 minutes after, 30 minutes after, than standard Nuprin, they could interpret it, and it would be more incentive to keep getting better, rather than have one criteria -- you need to beat a standard by ten minutes or more, and it doesn't matter -- you know, once you made it, you stopped looking.

Finally, I just want to -- Those are the comments I wanted to make. There's one question that Dr. Simon had about the -- It was really -- He said the dose response for pain relief with a sedative.

I think it's going to come up all day. The dose response of placebo pain relief has really not been studied. There's a real concern that I have that when patients get side effects from the medicine, pain relief is so suggestible that I observed in our chronic pain studies people -- and there are acute pain studies, too -- people do say they have pain relief with sedative effects.

We did one study where we looked at the dose response, and it seemed there was just a threshold with a slight side effect. They got a certain amount of additional pain relief, and the more side effects they had, there was no additional increase, but this is a very interesting question. It needs to be examined in 20 studies, not one study.

It's a real issue with the new wave of analgesics coming on. There is a danger of approving a drug that really has no specific pain relief action, just because it has sedative effects or some other perceptible effects. So that raises the issue of active placebos and a lot of other things that, I think, this afternoon might be pertinent for chronic pain.

CHAIRMAN PETRI: Other comments? Dr. Brandt.

DR. BRANDT: Question that relates to what you were just saying, Mitchell. Is there a correlation between side effects from a placebo and efficacy from placebo?

DR. MAX: Well, in that study that we did, which was actually a single dose study of a number of drugs in post-herpetic neuralgia, yes, in the placebo group the patients who got a placebo who reported any

side effects had three times as much pain relief as the placebo people who thought it was just a sugar pill.

CHAIRMAN PETRI: Other comments? Dr. Weintraub?

DR. WEINTRAUB: Mitchell, you mentioned that the individual patient responses can be measured by the technique that Dr. Laska has discussed. I'm wondering if both of you could offer your feelings, just how you're going to integrate the placebo into the individual patient responses and how you're going to -- how one would deal with the individual patient responses; because, you know, that's something we're very interested in at the agency.

DR. MAX: If you require as your baseline for a claim a comparison with, say, standard Ibuprofen, if it's a fast Ibuprofen product, you factor out the placebo response. Then I think the amount of placebo response in a study may still affect the outcome, made it more effective and somewhat less. So that's --

CHAIRMAN PETRI: I'm going to remind everybody to identify yourself before you give your response. Dr. Laska.

DR. LASKA: Laska. I'm not sure that I

agree with Mitchell, who I usually agree with, on factoring out the placebo response. I think onset time is like any other kind of measure. One has a measure for an individual.

Now the question is what is -- how to compare it to something else and under what circumstances does that make sense. Many believe that the effect of a drug is the sum of placebo response plus the little bit the drug adds on top of that. That's a model that may or may not be true.

In the onset time, the onset is the time that's observed. Factoring out some fraction of that onset time by subtracting the mean onset time for patients who get placebo may or may not make sense.

It's important to compare the onset time of a drug to a comparative that's meaningful. In the placebo case, as I mentioned in the talk, it's unfortunately the case that the placebo has very rapid onset, and it is not a condemnation of a drug in terms of its onset time if it fails to beat placebo, using the conditional measure as for those people who get the response; but I think you would have to demand that the placebo -- that the probability of response were somewhat superior to the placebo probability response or else there's no claim that's possible, in

my view.

CHAIRMAN PETRI: But we have a basic problem, don't we? The placebo response needs to be studied.

DR. LASKA: And it is included in almost every trial that's done in the analgesic world, but my only remark here is that failure to beat placebo in terms of onset time, particularly conditional on patients that get onset, doesn't teach you anything about the drug being ineffective; because you don't have to wait for serum levels to occur in that placebo response probably.

CHAIRMAN PETRI: Dr. Tilley.

DR. TILLEY: Yes. I guess that's what I was probably ineffectively trying to ask earlier, because it seems to me that, if we define then faster simply in terms of onset time that maybe that isn't the -- Maybe we're not asking the right question. I mean maybe our question is a broader question that includes both the probability of response and the onset time.

So we're being imprecise when we just talk about -- when we make those two synonymous.

DR. LASKA: Well, I think you're raising a critical point. It is what is the measure, what is

the way to characterize onset? If you look at all patients, what I call the unconditional analysis, you will reach the conclusion that the onset time of placebo is very slow, because, for example, the median onset time is six hours. It's at the end of the trial, but that's because most of those patients never responded.

So both are ways to characterize the drug, and they're both valid. Just one other point before you do your follow-up.

It's simple to imagine examples where you teach nonsense when you give just the conditional --

DR. TILLEY: Oh, I wouldn't -- I'm not advocating that at all. No, no. I mean, I think that your conditional approach is a much better estimate of what the true onset time is. I'm saying that, given that we measure it your way, that I think we're being imprecise perhaps to call that -- to just say faster only meaning fast alone.

In other words, I think without looking at the two pieces of it, the probability of onset and what you're measuring which is the best estimate of the onset time, and saying that the best estimate of the onset time is faster, we could be misleading ourselves.

DR. LASKA: If you give the values in terms of these conditional situations, then the time to onset is much shorter. It's a greater representation of the truth. The illustration is two drugs, one of which works in five percent of the patients, but it works in five minutes. That's a very fast acting drug.

If you do the unconditional analysis, it looks like everybody responds --

DR. TILLEY; Yes. I'm not advocating the unconditional analysis. I guess all I'm advocating is that, when we use the terminology, that we look at both pieces, the probability response and --

DR. WEINTRAUB: Dr. Tilley, can I say something. Actually, Dr. Soller this morning separated out faster as a comparative claim. We're dealing with fast, at least --

DR. TILLEY: Yes. I think I'm talking about faster.

DR. WEINTRAUB: Right. The other thing is that -- Well, I'll let it go.

CHAIRMAN PETRI: Dr. Yocum, and then Dr. Simon.

DR. YOCUM: Being new to this committee and my first meeting, I'm somewhat awed at this

discussion, because dealing a lot with pain is a multi-factorial issue, and are we going to have separate meetings then on intensity of pain and duration of pain and number of improvements?

It seems with the placebo response, fast seems to be a very difficult thing to put a finger on, and it seems like pain is really a multifactorial. Dr. Tilley has been trying to get at it, I think.

Sitting here, it seems that dealing with pain, while how fast it comes is important and in certain situations that's important, but I think most of my patients talk about the intensity of the pain relief, the duration of the pain relief, to come up with a composite score.

So that listening to this placebo response rate and that it's faster, gee, I think we should all just get OTC drugs that are placebo. It seems like it would be the greatest thing in the world.

So I guess, when the discussion started, I thought, oh, yeah, we should be able to measure fast, but in fact, listening to the placebo stuff, I'm not sure where we're going with this or whether we're going to be able to answer the question. But maybe I'm being very naive. I don't know.

CHAIRMAN PETRI: Dr. Weintraub wanted to

respond. Dr. Hyde.

DR. HYDE: Well, I mean, this discussion is really being motivated by proposed claims and already advertised claims concerning the speed of onset, you know, in a variety of areas, not just analgesics, but analgesics is confronting this, too. I mean, sponsors are interested in, you know, if they do have a better product, how can they, you know, get that recognized.

You know, they're doing studies to compare themselves to other. What recognition are we going to give to that? Do we recognize that as something clinically meaningful that we -- or do we just dismiss that? I mean, we have to confront when we get these data what are we going to say about it? What will our position be on it?

DR. YOCUM: So we can't stop people from putting in -- It seems like we can't really define fast, but does that mean we can't stop people from talking about how fast things happen?

CHAIRMAN PETRI: I think Dr. Laska wanted to respond, and then Dr. Simon.

DR. LASKA: Dr. Yocum, I think you haven't characterized properly the conclusions that I hope the committee can reach from the discussion, and probably

the difficulty of some of these concepts or the lack of clarity of the presentation.

Placebo is a good thing to use, if you are one of the ones who it works for. Unfortunately, it doesn't work for most people. So I wouldn't recognize that as the OTC drug of choice, and I think the presentation is meant to argue that you can define what fast means and what faster means.

The issue is where to draw the line, whether fast is something that one would have to characterize as being beating something else or whether one would have to characterize it as having some properties at least as good as or at least as fast as.

The debate is on the nuances, not about whether it's doable.

DR. YOCUM: But it would seem then you would need to eliminate the placebo response responders in your studies. Otherwise, you --

DR. LASKA: No. No. Placebo response is a real phenomenon. Patients who receive placebos respond, some of them, and when they do, they tend to respond rapidly. That's a fact. It doesn't change the issue associated with the fact that there is more patients who respond to an active drug, and when they

respond there's a whole distribution over time as to when that takes place.

CHAIRMAN PETRI: Dr. Simon.

DR. SIMON: Perhaps Dr. Weintraub can help me with my naivete, based on my academic rather than commercial background.

I'm a little troubled by the pejorative question of fast or faster as opposed to how the evidence might be seen. If we can do something that's measurable with an inadequate instrument, but it's the better instrument that we have now compared to what we had previously, whenever that instrument comes up, that might even be better two years from now; but if we can measure something and we present that evidence within any document, advertising or whatever, it seems to me this is really not a question of safety.

It's not a question of real efficacy. It works. It's pain relief. Question of speed of onset is implied in a pejorative manner by saying fast or faster with a stamp of approval.

Since these are OTC products and since patients -- this is really a commercial question of one being better than another in a way that's inadequately measured based on the technology, but it's the best technology we have, why do this?

DR. WEINTRAUB: I believe that fast is an aspect of efficacy. The onset of pain relief in this case, were it bronchodilation or anything you can name, sometimes has an important effect, and part of the whole response to an analgesic is the speed with which you get -- you may be able to get a response.

Now I know Dr. Tilley is going to say again we should be taking in how many people take it, but it is an aspect of efficacy. Dr. Yocum, we are already measuring other -- the integrative things that your patients are telling you. We are already doing that, but we're just now concentrating on that initial part of the curve, so that we can measure fast and meaningful relief.

DR. YOCUM: I presume maybe I'm getting educated here.

CHAIRMAN PETRI: Dr. Yocum, please remember to identify yourself.

DR. YOCUM: I'm sorry. Yocum. -- that we might have a statement then that drug X shown to improve pain in X percentage of patients in X minutes compared to placebo, if we're going to -- but it seems like we're going to have to include placebo. Am I wrong?

CHAIRMAN PETRI: Well, perhaps not if the

placebo was a very small amount of the effect. Dr. Tilley?

DR. TILLEY: I guess I'm still wondering, along with Dr. Simon, why we have to use the word fast. Why can't we do, as Gene suggests, which is say X percent of the patients had an onset of pain relief, and others who had an onset of pain relief, it was in X amount of time; and get away from fast or faster?

CHAIRMAN PETRI: Let me ask Ms. Malone as our consumer representative, what will the consumer understand?

MS. MALONE: Well, I think, when they see fast or faster, they think, oh, good. You know, like this is what I'm looking for. You know, I don't want this pain anymore. So I think the term really is an advertising and a selling point, and I think people look at it probably in the range of like 15 minutes to a half hour, you know, like no longer than that, when they see the term fast.

CHAIRMAN PETRI: Dr. Weintraub.

DR. WEINTRAUB: The main reason why we're looking at it is because of just what Ms. Malone just said. If we don't look at it that way -- let's say if we make it minutes or report it in minutes, then you have the unfortunate -- or I believe to be unfortunate

slicing of the salami ever thinner, you know, until that slice is really thin.

What do I mean? Seventeen minutes, 16 minutes, 15 minutes. In the next trial will come 13 minutes, and we'll be fighting that battle over and over again, but the conditions won't be the same. The patient population will not be the same. The disease will not be the same. Fortunately, the drug will -- the drugs may or may not be the same.

So, you know, we're looking at many different aspects, and we're talking about making ever narrower cuts, and we're faced with that issue right now. I could ask Dr. Katz to elaborate on that, but -- you know, because there are some things in the OTC realm where we're facing that right now.

We're also facing it in things like migraine headache relief medications, which are said to be an hour and a half or a half-hour, and already they're starting to cut. Look, some things start to work before the drug has a chance to dissolve.

CHAIRMAN PETRI: Dr. Callahan.

DR. CALLAHAN: Do you have different definitions of fast based on the disease or is it just one definition of fast?

CHAIRMAN PETRI: That's going to be our

topic. Dr. Max.

DR. MAX: One issue is, however you set up the criteria, companies are going to try to manipulate the design of their trials to meet it, and you want to make sure that the way they manipulate it -- you know, which is an appropriate thing -- is one that will give the consumer meaningful information.

A problem, if you just have a time of onset, like if you say you have to have onset in 30 minutes to be fast -- What I would do if I had a company would be to take people with the least pain possible, with very slight pain, say, having a baby tooth fall out by itself, and we know then that anything you give -- you know, whatever drug, analgesic drug you give them will beat placebo, and it will be a very spurious example, because that isn't what the consumer wants to know about. However, if you require some sort of comparative difference saying you beat the Federal Bureau of Standards Ibuprofen by ten minutes, you can't do that.

If you take very little pain, both active drugs, a placebo may not be so good against these very weak pains. It will be a little bit better against a weak pain than a strong pain, but if you take the weak pain and take two active drugs, you'll never separate

them.

The way a company will try to separate two active drugs and show you beat your competitor is to try to get lots and lots of pain, because there the mediocre drug will fall by the wayside, and the strong drug will work. So that's one argument for doing comparative rather than an absolute time.

CHAIRMAN PETRI: Dr. Max, I think the point you made earlier is important here, that it depends on the pain model, dental pain, dysmenorrhea pain. I think that disease process is going to be crucial, not just the amount of pain.

Dr. Liang.

DR. LIANG: This may be a stupid comment, but why can't you standardize the assay system and make that as part of the minute.

I'd like to see numbers rather than adjectives myself, and as long as you told me what model, I wouldn't care. I mean, that would be a basis for comparison. Maybe dysmenorrhea is not a great model for RA or whatever, but at least it's some way to calibrate by way of example.

CHAIRMAN PETRI: Well, why couldn't we have an OA model?

DR. LIANG: I don't know if people would

be able to agree, but I don't think it matters, as long as you sort of standardize it.

CHAIRMAN PETRI: But maybe it does matter. Maybe something is faster for migraine than it is for OA.

DR. LIANG: I understand, but you know, you have -- In two watches you can't tell the time. You need to have one assay, and you know, if someone who were able to give you yet another number for RA, OA or dysmenorrhea, fine; but if you had one assay system, I think the world would be vastly improved, from my point of view.

CHAIRMAN PETRI: Dr. Simon.

DR. SIMON: I'd like to throw my two cents in, whatever it's worth, on that particular argument, because in fact, I think, Michelle, the point of having different technologies that then measure different kinds of pain and then expressing it in a quantitative time fashion as a response is the only way to do this, because of the issues associated with OA pain which are different than migraine pain, which are different than inflammatory driven pain, and because the responses would be entirely different, based on what the biological reason why the drug works, that the only way to compare would be to know

(a) the model that it is being used in, and the only way then to apply any kind of pejorative adjectives would be to know, in fact, what the exact time sequences is to response.

That may actually help with this lack of placebo understanding as well, since each of those areas will have its own placebo response continuum that would then modify how you would interpret the data.

CHAIRMAN PETRI: Dr. Yocum.

DR. YOCUM: Yocum. That would, I think, work well for prescription drugs, because they are trying to get approved for a certain disease entity. So there's probably a lot of data on onset of action, but OTC drugs are aimed at a whole lots of different areas.

So it seems almost impossible unless you're to -- you know, the patient pulls down a little list and downscrolls; let's see, migraine --

DR. SIMON: This seems even more impossible -- Simon. This seems even more impossible.

CHAIRMAN PETRI: Let me have Dr. Hyde perhaps remind us all about the pain labeling, which does mention pain models.

DR. HYDE: Well, I have another comment.

There is sort of a precedent, in a way. What we've done so far for analgesics -- some of the NSAIDs are labeled for analgesia, and some aren't, and the criteria we have was basically, you know, an adequate onset of action, usually separation from placebo by an hour and an estimated time of around a half an hour or so.

So, I mean, there is sort of -- This is -- something like this has been in effect for a while, at least in the prescription analgesic area, and translate that to anything that goes over the counter would have to be analgesic and have at least an adequate onset of time.

So, you know, we're talking about now a modification of this. We've, you know, rigorously avoided putting specific times on that to avoid the burger wars thing, you know, 17 minutes, 16 minutes. You know, how do we really standardize that.

While we do have good models, I'm not sure that they are so good that they can, you know, stand up to -- You know, you can always do another trial and get it a little better; and if they aren't, you know, quite in as much pain -- You know, so if we're going to, you know, give an absolute time for something just to study this drug and get a time for it, you know, it

would require a level of standardization I'm not sure we're quite prepared to provide yet.

CHAIRMAN PETRI: Dr. Tong.

DR. TONG: This is Ted Tong. I'd like to add to Dr. Yocum's comment about over-the-counter medicines. Our group, I guess, about a year ago looked at migraine, and we know now in over-the-counter analgesic medicines there are ingredients in there that are not exactly in the category of analgesics that probably serve to enhance the pain relief and maybe actually speed it up, and I'm thinking of something that we drink around the table here, caffeine.

So the other issue then also is, when we're looking at these various models, we have to put it in context in which the OTC is going to be selected by the patient, and the decision about fastness is influenced by other things.

CHAIRMAN PETRI: An excellent point. Dr. Harris.

DR. HARRIS: Can I ask just for my own edification, how precise are these time measurements? I mean, if one says 13 minutes. I guess it depends to a degree on the size of the population you are measuring, but if you said 30, could it be a mean time

of 13 and could it be 15 or 16?

CHAIRMAN PETRI: Can we take the dental model and just give us, you know, the plus/minus, Dr. Laska?

DR. LASKA: I think you have to be very careful about characterizing the time event with one number. The number that you've described is the median time of a very big distribution. That means that something like, let's say, 10 percent of the patients get their response in the first 15 minutes or whatever, and the last part of that group don't get their response until two hours.

So this is not like a traditional -- at least our experience yet hasn't proven that this is like the traditional normal distribution theory situation where you've just translated the time a little bit to the left or a little bit to the right.

So it's not easy to give an answer to the question, is it 13 minutes or 14 minutes. Certainly, there's no certainty in these observations, regardless of the sample size, that will allow you to reach that conclusion.

Nevertheless, I think the idea of telling something about the properties of the parameters to the public is a good one, and it certainly beats the

-- even though you're in nonstandard situations, you can give ranges. The median time to onset in ten studies ranged between 20 minutes and 40 minutes.

Those are the kind of information that truly teaches what's going on, and if you make it disease specific or etiology specific, there is information the consumer will get that's valuable.

CHAIRMAN PETRI: These distributions are not Gaussian?

DR. LASKA: I doubt it. Certainly, they are not, because Gaussian distributions tend to be, for example, negative or positive. These numbers are all positive. Some say they are Weibel distributions.

DR. HARRIS: Could I --

CHAIRMAN PETRI: Dr. Harris.

DR. HARRIS: Yes. Sorry. Could I ask a follow-up question. Suppose you did get 20 percent responders in ten minutes, and you repeated this again and then somebody else in another study, same drug. Would it be likely that you could have easily gotten 40 percent responders in five minutes; in other words, a completely different number?

DR. LASKA: I wouldn't say anything that dramatic, but there's certainly variation from study to study, for sure, and that's also true in efficacy

measures. That's the argument people use to sound like it's comparative.

Within this trial, I can tell you that drug A beats Drug B. Within another trial, different circumstances, different patients, different severity, Drug A also beats Drug B, although the amount that it beats it by is different.

The same kind of thing is argued and will go on in this circumstance. The trouble with the analgesic trials that are based on pain effect levels is that I can't really report to you the mean Spitz score or the mean Tochbar score. It just has no intellectual or clinical sense. It doesn't provide any information to you, but the time to an event does.

So it's new for us in the analgesic field. It's new, because the measures have a human understandability. The others are artificial, and the debate is, well, should we give people these numbers, because maybe it's only comparative that means anything, versus here's real information on time to onset.

My personal vote is give out the information.

CHAIRMAN PETRI: Dr. Tilley.

DR. TILLEY: Also, I just wanted to remind

people that you wouldn't be saying one drug was better than the other, because there was a difference in a minute. I mean, you would be using statistical methods, just like you would be comparing any two distributions to see if they were differences that could have occurred by chance.

So, you know, it isn't going to help you to say that your drug is 17 and the other drug is 18, if there's really no difference that you can show statistically.

CHAIRMAN PETRI: Dr. Katz.

DR. KATZ: You're probably right in one sense. However, it's the advertisement that becomes a problem, and that those time differences do become a source for advertisement, and it's a source for claims in commercials, and everybody who's ever watched commercial TV has seen -- even though they're not allowed to make comparative claims, different companies making comparative claims over different over-the-counter products on the basis of what we allow in labels.

So that what we put in the label with regard to a claim is critical, because it gives a source for advertisement, whether it be true or not true, and how it can be extended.

Going along with some of the discussion about time and what does time mean, fast, what does fast mean, whether we're talking about -- We need to go back to look in terms of a consumer's perspective, because I'm not sure that a consumer really defines fast in the same way that we as clinicians may define fast, that we maybe think that it's more important to have time to onset; whereas a consumer might think it's more important to have time to relief.

So when we're labeling something as fast and we're thinking that we're doing someone a service by saying, yes, this is fast, because we're thinking of fast onset, what the consumer really themselves might be interested in is time to relief, and could care less if they have a faster onset but it takes longer for them to get complete relief with one product versus another product.

CHAIRMAN PETRI: Dr. Liang first, then Dr. Max.

DR. LIANG: This is just a question. I heard one presenter say that the FTC is the one that beats up people who use inappropriate language. Is that true? You don't actually do that.

DR. KATZ: We do not. Once a product goes over-the-counter, after the initial launch the

advertisement is controlled by FTC. However, FTC usually will not go after someone unless what is being said is really terribly egregious.

So that, unless there are a variety of complaints or they see something that sounds like it's really terribly egregious, that it remains.

DR. LIANG: How do they do it? I mean, how do they do it now, specifically on fast or fastest?

DR. KATZ: Again, if they feel that an advertisement is really out of line with relation to the labeling that they have or what they know about the product, they will come back to the FDA to ask us if there is basis for those claims, and then depending upon what information we give them, determine what action they may or may not take.

DR. LIANG: I think that we have so much better use of our time and money than to look after this. I mean, I don't think the public really gives a damn about fast, faster, fastest.

CHAIRMAN PETRI: Dr. Liang, let me have Ms. Malone respond. Of course, everybody on this panel is a consumer of analgesics, but I'm going to ask Ms. Malone to respond.

MS. MALONE: Okay. As I said before, I

think they do take into consideration, when you say fast. I mean, it's a catch word, you know.

DR. LIANG: I think everyone is using it to the point that it has no meaning anymore, and this morning is an example of it.

MS. MALONE: It's like what Dr. Ehrlich said. Fast may get them to initially try it, but if they're not getting relief, then it, you know, sits in your medicine cabinet and, you know, it's there for ten years and you eventually throw it out, and you'll try something else. But it does initially get them to try it, I think.

CHAIRMAN PETRI: Dr. Liang, our charge is to make it have some meaning. Dr. Max.

DR. MAX: There are several -- I tend to agree with Dr. Liang's suggestion that we give -- if we give information, we give absolute numbers, because the public can use them intelligently. There are several types of information, however.

One thing is someone who takes a pill wants to know when it's time to give up on the pill and take another one. So that's in the conditional relief that Gene was talking about.

If you haven't gotten relief by 60 minutes, you're unlikely to get relief, and those are

under real world conditions. People have commonly eaten, for instance. However, the best -- If you want to do a horse race, if you want to have a standardized comparison between two drugs, as we said, the most efficient way to do it might be in fasted patients in the oral surgery model, and commonly compared to like dysmenorrhea studies where people have often eaten or tension headache studies.

You see onset for an NSAID of 60 minutes. You may see them at 20 minutes for a rapidly dissolving NSAID in oral surgery, but if you put on the label this gives relief in 20 minutes, the consumer who has eaten, who has a cold, who has a sore throat, etcetera, will be misled and may give up on the medicine and may overmedicate.

So it will be a real tricky issue as to how you get this information or how you address these two needs without confusing the consumer.

CHAIRMAN PETRI: Dr. Simon.

DR. SIMON: At the risk of being redundant from yesterday, I'd like to quote Dr. Ehrlich who suggested that perhaps the measurable drives out the important, we have to have that everyday to remind ourselves what's going on.

I'd just like to ask the question, whether

it's possible -- Because clearly we want to define fast and faster, is it possible that we could define parameters or regions that one would fall into being fast versus faster, and that that way we would get away from the problem of specific 16, 15, 14 minutes, and that way you have these ranges that one would consider that would fall into that category, so that we would achieve the needs of the FDA and achieve the needs of the commercialization of these products?

DR. WEINTRAUB: Yes, it is possible. We asked -- We're going to ask you later this morning, perhaps after we have a break --

CHAIRMAN PETRI: Really subtle.

DR. WEINTRAUB: We were going to ask you to discuss that very issue, because, you see, we want to integrate practically all the things that have been said this morning. You know, I would put Linda or John on the spot and say don't they agree with most everything that has been said this morning, and the answer is yes.

We want to integrate them. We want to come out with something that is meaningful and most helpful, both to the consumer in the over-the-counter area and to the person who takes a prescription drug and the physician who prescribes it.

CHAIRMAN PETRI: Dr. Fernandez-Madrid.

DR. FERNANDEZ-MADRID: I think I was going to make the same motion as Lee did. I think this is, it seems to me, very futile to study all these products to define them in terms of 17 minutes or 21 minutes, five minutes more or five minutes less than another one.

So I think defining fast as a range of responses makes, to me, much more sense. In that way, you would eliminate the rat race of the minutes, and perhaps you could also eliminate the faster concept, because I think to produce data with significant difference between minutes doesn't make any sense to me.

So -- but this would eliminate slow acting analgesics that we know take four hours, six hours, two hours, but it would define the range as fast. It may suffice to do it.

CHAIRMAN PETRI: Dr. McKinley-Grant.

DR. McKINLEY-GRANT: Lynn McKinley-Grant. Have there been any studies where consumers have defined what fast is, of people who have the different -- you know, I'll call them over-the-counter pains. Maybe we should do a study. I mean, just ask people. I mean, migraine, they need something in five minutes.

For dermatology, for itches, you need something in one minute, but -- I don't know if any studies have been done on that.

CHAIRMAN PETRI: Does anyone have any knowledge about that?

Okay. Now this might be a good time to take a requested break. We'll have a 20 minute break, and then reconvene.

(Whereupon, the foregoing matter went off the record at 10:00 a.m. and went back on the record at 10:20 a.m.)

CHAIRMAN PETRI: Now I promised Dr. Blewitt that he could make the first comment after our break.

DR. BLEWITT: It seems a good time to do it, because nobody is here.

I think that doesn't it really get down to sort of I'll know it when I see it, and it seems to me that we've been dealing very much in a data vacuum today.

I don't know how it's possible to make any sort of a judgment, particularly on comparative claims, without seeing some sort of data to -- in order to understand better how these data were derived. It's a very complex issue.

We've heard today, for instance, that dental pain is a good model for onset studies. Well, what does this mean for other types of claims? What if you want to claim headache or dysmenorrhea, and how do you then state these claims?

So it's such a complicated issue, but what makes it more complicated is not really seeing any data at all. So in a sense, we're dealing in the abstract. It seems to me that, if you take it on a case by case basis, it's a much easier judgment to make, you know, under those conditions.

CHAIRMAN PETRI: Obviously, your point is well taken, but I think what we've been charged as a committee is to take a stab at this. In the wisdom of the committee, there may be some common sense that we can apply to a situation even without any data.

DR. BLEWITT: I would make another point. Well, it then becomes highly arbitrary. Obviously, if you assess any sort of a number or even a range of numbers, it becomes all the more arbitrary without the data.

In addition, I would just say, too, that if -- For instance, if the agency is looking for numbers, it probably invites more problems than if they didn't have them, because then you're -- If you

say, well, you know, it's X time, that means fast, then you will now have companies who say, well, gee, you know, we're faster than that. So we're going to say we're fast or faster.

So you know, to try to set some sort of standard without knowing the overall context is very, very difficult, if not impossible. So that's why I say on a case by case judgment, I think it's better done that way.

CHAIRMAN PETRI: Dr. Yocum had a comment, but then I'm actually going to ask if we can direct ourselves specifically to the questions. I think that will help to focus the discussion. Dr. Yocum.

DR. YOCUM: I guess prior to the break I, too, was going along the line that Lee had talked about of making ranges and defining them. I guess, in relationship to the most recent comment, was are we expert enough in pain to define those ranges? Are we the people that should be here doing this or defining those ranges, or should you convene an expert panel of pain people to do that? Naive question again.

CHAIRMAN PETRI: Now we in rheumatology are experts in pain. We'd like to ask Dr. Koda-Kimble first, because she's been patiently waiting.

DR. KODA-KIMBLE: I want to go back to

something that Michael said early, and he says, well, I think that fast is part of efficacy. So I do think that, when we as a panel -- I'm speaking from a nonprescription drug perspective, that as a panel member it seems to me that what we need to do is distinguish between acute and chronic, and that we could say, for example, that any drug that shows us that they are effective for acute pain -- and it seems to me as part of our efficacy discussion we would be looking at onset in the instance of acute pain -- could, by definition, say they're fast; because it seems to me, we would not allow a claim for acute relief of pain if something didn't respond in a fairly, reasonably fast manner, whatever that is.

CHAIRMAN PETRI: There's that word fast again.

DR. KODA-KIMBLE: There it is. Well, I mean, I think that the panel needs to consider that in its definition of efficacy. It also is something that we need to consider in our definition of safety, because if someone sees a product that has a claim to be effective for acute pain and they don't get a response in what they would consider to be a reasonably quick manner -- and I don't know what the consumer or what even the panel would consider fast in

that case -- they have a potential to overdose on these medications.

So it may relate to a claim that is allowed as opposed to, you know, tying the fast to the claim.

CHAIRMAN PETRI: Dr. Weintraub.

DR. WEINTRAUB: Dr. Petri, you answered Dr. Yocum the way I was going to. This is our expert panel on pain and on OTC drugs. But more importantly, this, remember -- I did say, I hope, that this was an early effort to try and get our hands on pain. It's going to move very fast, because of -- That was a bad choice.

It's going to move -- There's no way to say that -- with all deliberate speed. It's going to move fast, because of so many parts of the agency being involved in what's fast.

Now the second thing is, I agree with Dr. Koda-Kimble. The issue as part of efficacy is not just the speed -- is not just fast, but it is onset. What we want to know about a drug is when does it start, when does it reach peak effect, and when does it stop or when does the effect start to go away.

I mean, those are three important time points that everybody has to -- I mean, we teach our

students in pharmacology that those are three important things to ask about every drug, and what we really want to know is how long is the plateau at the top. We'd love to know that as well.

So I see it as predominantly an efficacy question, but also as a safety question, and it's not just for overdosing accidentally or deliberately, but it's also for a variety of other things that a patient has to know.

That's why I like what Dr. Max said about giving us individual response data, because a patient has to know what are their chances for getting a certain response at a certain time; because with that knowledge, armed with that knowledge, they can make good decisions about when they have to repeat the drug, when they can expect the beginning of the offset of the drug, etcetera.

So with those things, people can be much better educated, whether it's an Rx prescription or an OTC prescription. They can be much, much better educated about the drug.

CHAIRMAN PETRI: As we move -- Dr. Ehrlich first. Then we'll move to the questions.

DR. EHRLICH: Thank you for giving me a chance to rebut Mike.

I certainly agree with Dr. Weintraub that peak effect and duration of effect are very important things. Onset is a very complicated matter, however. I firmly believe that the onset, as defined by when you first experience relief, probably is placebo effect even for the drug, because most people claim that they're beginning to see responses before the drug has even had a chance to absorb.

So I think that that's not a meaningful concept -- as meaningful a concept as when you bring the pain level down to some proportion. But I think what the difference is between prescription and OTC is who the consumer is.

In prescription drug, the consumer is really the learned intermediary, be it physician, pharmacist or whoever, and that person makes the decision for the person who is buying the medication or for whom the medication is prescribed as to what it is that you're trying to achieve, and you know whether you're going to do surgery, so that the pain begins at a finite time, or whether you're treating some chronic pain where there's constant pain.

On the other hand, for the OTC products the consumer is the person who is buying it. There is no learned intermediary in a supermarket. You go and

you pick something up, and it depends on what you're experiencing.

Obviously, if you have gone to the dentist, you had an extraction or a filling or whatever and you think you have pain, you're going to take it immediately. You know when it started.

With headaches, I think all the people around the table have had headaches or have had muscular pains and so forth, and sometimes you've just waited and decided it will go away by itself, and then it continues to rise or it continues to stay, and you're tired of it. So you decide, well, I'm going to take something.

Then you want some relief. Now I did an informal survey before I came down here, not in this room. No, before I came here from Philadelphia, I did an informal survey amongst my acquaintances. How do you define fast? And knowing that we were going to be discussing this, how do you define fast when you take something?

I even asked my wife. The answer was, well, I sort of -- within a half an hour, I'd like to feel better. That's a somewhat vague definition, but I think that's the best we can do, and I think that to micro manage by giving numbers to the consumer for OTC

is probably incorrect.

On the other hand, I don't mind some micro management in numbers or the like to the learned intermediary who can interpret this, because the learned intermediary knows what condition is being treated and what that person wants to achieve; but when we take something on our own, and all of us are consumers in those cases before we become patients, obviously, we've decided that we need some relief, and each of us has a different definition of what that relief is.

I don't think a specific number on the label or even where segregation into different syndromes is very helpful under the circumstances.

CHAIRMAN PETRI: I'm going to force us to move on, and I hope this will be appropriate to some of the questions. So you will get a chance.

I may take the chair's prerogative now and reorder the questions. I actually want us to start with the second question first, because it's a concept question. I think, if we don't agree on the concepts, we're going to have problems later on.

The question is: Should fast be measured clinically in terms of: onset of any effect; meaningful or substantial relief; pain half-gone; pain

completely gone. And I'd like to add the thing I brought up this morning. Is pain relief wearing off, although I'm very willing to redefine that. So when does the person need to take something else?

We've already had disagreement this morning. Dr. Max preferred having the many choices, a Laekert type scale. We have a lot of reading, and it's been brought up this morning, all these problems with the onset effect, that that may not be measured very accurately doing the two stopwatch techniques. The problem is complicated perhaps by placebo effect.

Why don't we start with that? Is it important to measure onset of any effect? Will the consumer get the information that he or she needs by some of these other concepts?

If I could have committee and audience input about onset. Dr. Simon.

DR. SIMON: Yes, no, no. Basically, I think that it's important, if we had a methodology that could do it. We've already admitted that we can't, because onset is too difficult to measure, and there are too many confounding influences.

So, therefore, yes, it's important. Should we measure it? No. Should we define it? No, because until we have better technology and

methodologies and until we really understand actually how these things affect pain from a biologic point of view, I don't think it's a doable process.

CHAIRMAN PETRI: Dr. Max.

DR. MAX: Here we suffer from not having 30 clinical trials in front of us. I think you would see, if you looked at 30 clinical trials of dental pain and headache, etcetera, that you can pick up common OTC nonsteroidals compared to placebo or dose response in terms of the onset of meaningful relief or a lot of relief or some relief or pain half-gone.

It's really the methodology that Gene outlined is just fine and agrees with the previous methodology that 15,000 analgesic clinical trials have been done, except it provides additional individualized response. So --

CHAIRMAN PETRI: Dr. Simon's point was only about this onset, the --

DR. SIMON: The first, perceptible?

CHAIRMAN PETRI: Yes.

DR. SIMON: It's clearly -- I'm reading the question as meaning the onset of pain relief. I presume --

CHAIRMAN PETRI: So we won't discuss meaningful pain relief. That's going to be a separate

DR. LASKA: We'll call it by its name here, perceptible relief. That was confusing in the discussion to me.

CHAIRMAN PETRI: Okay. In some of the literature it was also called onset. So I realize that these terms don't have necessarily agreed upon definitions. So perceptible pain relief is on the table right now. We basically need to reach a committee consensus about whether this is important.

Dr. Simon's point is that it's not easy to measure. There are confounding variables, placebo effect. Other thoughts?

Let me ask specifically Ms. Malone. Is onset -- perceptible pain relief onset -- is that important enough to the consumer that we should keep this concept, even with these measurement problems?

MS. MALONE: I think it's used more by the advertisers. I think, you know, the patient is obviously looking for meaningful pain relief, but I think it's what, you know, you see in advertising, and it's the onset of any relief or anything going on that the advertisers claim.

You know, they always have the disclosures down at the bottom, you know, where you can't read it, and they will give the time. It may vary, etcetera.

I think a large part of the problem is the semantics, like we're using all these terms and no one has agreed -- like you could use fast if everybody had the same definition of fast. You know, all of these things mean different things to different people.

CHAIRMAN PETRI: But I think our problem here is that fast can be applied to each of these concepts. So I'd like us to decide first which of these concepts of pain measurement are important. What is important to the consumer?

MS. MALONE: But what I'm saying is that the consumer has to be aware of what you're talking about.

CHAIRMAN PETRI: Exactly. We're going to have to define these so that John Q. Citizen understands them. We're having problems on the committee understanding them.

Hearing no other comments, the next concept, meaningful or substantial relief. Dr. Ehrlich also redefined this as when does the pain become tolerable. I'd like to have committee suggestions about the importance of this and how to define it for the consumer. Dr. Max, in the dental pain model?

DR. MAX: As I said, the results with

meaningful relief, some relief, pain half-gone, generally agree is a robust measure. I actually need to make a slight retraction.

I said before that Gene and Al's term of meaningful might be repugnant to some psychologists. In our group there are three people who devised our scale, but one of them, Patsy McGrath, says she really likes meaningful. So I think they're all good.

CHAIRMAN PETRI: Let me ask Dr. McGrath for comments on defining meaningful for patients. Shall we perhaps have a litany of terms that are synonymous with meaningful?

DR. McGRATH: Patricia McGrath. Mitchell and I had just talked for a moment, and I'm answering this question from a person who uses OTC products as well as a person who treats pain patients and discharges pain patients when they successfully reach goals.

Recognize that pain is subjective. It's fascinating, and this morning has been very exciting from a pain perspective; but meaningful is really tied to the individual sufferer. When you discharge a patient with a particular pain related to a disease or health condition, they make a distinction with the therapist about what treatment goals have been

successful.

It is not always a specific drop in the pain intensity value. It may be that the quality of the pain has changed, its aversive component, their ability to manage and be less disabled by it.

I think that the person with the pain problem is the best judge of what is a meaningful difference in their pain level, and meaningful may be a terminology that helps to wash out the variability in the different kinds of pains that we referred to this morning; because what is a meaningful reduction when someone is pulling out my third molar is very different than a meaningful reduction when I have a headache at the start of a busy work day and know that something can take the edge off it and I can then move forward and the other things of the day will block the pain.

So I would like to work more from a meaningful distinction than a particular number value, and I would also like to link it to some of the data and the exciting models that we've heard about today. I don't know if that helps.

CHAIRMAN PETRI: Let me ask the committee, though, because I'm not sure that every person in one of these pain studies will understand what meaningful

is. Already here, we have meaningful or substantial. Should we have an "or pain has become tolerable," as Dr. Ehrlich suggested? Dr. Laska?

DR. LASKA: I don't think is a voting issue. This is an issue on the judgment on what has worked in the past, and there have been many, many trials now for which this meaningful word has been used, substantiated by research by one of the next speakers which vitiates the question of whether people understand it or not.

They may or may not understand what it means to have moderate pain either, but we go ahead with these clinical trials, and we do the best we can explaining the concept.

CHAIRMAN PETRI: Well, you are advising us to take out the "or substantial." You think it should be "meaningful." That's it?

DR. LASKA: I don't think this is a voting matter. I think it's an issue which will --

CHAIRMAN PETRI: We're not taking a vote. We're asking for clarification. What we've been asked to discuss is meaningful or substantial, and you're advising that it should just be meaningful.

DR. LASKA: No. I'm advising that meaningful has worked very well for the past six or

seven years. That's all.

CHAIRMAN PETRI: Audience comment at the microphone?

MEMBER OF THE AUDIENCE: Yes. Dr. Desjardins from UMDJ once again. We specifically asked that question to a group of 60 patients who completed the questionnaire using commercially available Ibuprofen and placebo.

None of the 60 patients had difficulty defining meaningful in their own terms. We did an exit interview and said how -- what did this actually mean to you. For most of them, it's when I didn't have to concentrate on the pain anymore; I could think about doing something else or I could go back to doing my reading or other activities.

It has not been a challenge for patients to understand meaningful. In addition, when we asked them how confident are you when you stop that stopwatch that you really had pain relief going on when that occurred, and you rate that confidence from zero to ten. The mean score for those 60 patients is up in the 8.3 or 8.4 range.

So again I would echo Dr. McGrath's comments, that patients can define this themselves. To the extent we as clinicians try to define that,

we're putting the data through another set of filter, another set of eyes.

CHAIRMAN PETRI: Dr. Max.

DR. MAX: I want to point out that there are two different aspects of the innovation that Gene and Al and their colleagues introduced. One is to hit a stopwatch to say you had reached a certain criterion. The other is to use individual techniques instead of means to analyze things by survival analysis.

Now many of the trials that I've looked at have taken the regular interview, say, every 15 minutes in the first hour, where patients are asked about pain half-gone, is your relief slight, some, a lot, etcetera. So using -- You could use the survival analyses techniques with those, and they all -- the terms at the middle of the scale, half-gone and some, and a lot, come out similar to meaningful did on the stopwatch.

Meaningful -- Gene is absolutely right, that if you include the stopwatch, which gains a little bit of additional precision, especially if you don't have a nurse there every ten minutes, the only one that has the track record with the stopwatch technique is meaningful. I mean, we can speculate on

others, but if you want both of those features of the innovation, you know, I think it's absolutely right.

CHAIRMAN PETRI: At the microphone?

MEMBER OF THE AUDIENCE: Al Sunshine, New York. Dr. Johnson raised an interesting question on the hypothesis that -- of how to measure onset and relief, and he pointed out that it should be tested.

Well, there is a body of data. Probably the largest body of data is with Michael Weintraub and his associates who have seen this question approached in many different ways.

There is also data in the literature, and I agree with Dr. McGrath that the approach or the use of meaningful, which is the method that we proposed and we have used, has the patients interpret for themselves what is meaningful relief.

We don't -- and I don't think this is the time to bring in new parameters. We ought to look at the parameters that have been studied. Meaningful -- The word -- The responsive of patients to meaningful relief does yield data that's consistent with PK-PD determinations, with dose response, and fits the clinical picture.

Perceptible relief -- there's a body of data, and Paul Desjardins who preceded me has pointed

out that this is not as robust measure as meaningful relief. So I think that the committee, perhaps with the help of the FDA in looking at blinded material, could really get -- There is data on this, and it's not a question of opinion. I think it's a question of fact.

There's one other point, I think, and I don't know if it's come across; but Dr. Tilley and I spoke about that. Gene's approach as to the first question is: What is the probability of response to a treatment? And you get a value. Placebo has a 40 percent probability, and active drug has 100 percent.

Then the next question is: If you respond, what is the time, the length of time, it will take? Now one thing that hasn't been brought out is response time is dependent on a variety of factors, but one very important one is the disease entity.

Headache, dysmenorrhea, dental pain all have different response times. So that there is no -- This idea that there's an absolute time -- I mean, that's dream world. There is no absolute time, be it 15 or 17.

There are other comments I have, but it has nothing to do with onset. Perhaps later I can comment.

CHAIRMAN PETRI: Okay. Thank you. Dr. Soller has a comment.

DR. SOLLER: Yes. I just had sort of a referencing comment. I've been before advisory committees where I've said, now we're talking about the consumer, and reminded the advisory committees that we're not talking about patients.

I find it interesting that the orientation here is that we're talking about consumers, and I hear that over and over, and from the audience I'm hearing patients. As you're thinking about the specific parameters, I think there are three pieces here.

There's the health professional, which I've yet to hear about. What is that you want as practitioners, and what do you want to have measured, and what do you want to know about the drugs, which might be different than what is translated to the patient, and might be quite different. As we break up fast and faster, we'll be talking about that as it would go to the consumer.

So I think it is multi-tiered.

CHAIRMAN PETRI: Thank you. Now the next two concepts we have on our list are pain half-gone and pain completely gone. So Dr. Simon?

DR. SIMON: Because my question actually

will relate to that as well, could Dr. McGrath please explain to me: In thinking about goals and establishing responses and meaningful, and it also relates to this issue as well, there must be differences in chronic versus acute pain and how you think about meaningful relief and chronic? Yes, no?

DR. McGRATH: Yes, there are, but I thought that should wait until this afternoon. I can comment. I felt that discussion right now as relating more to acute pain.

DR. SIMON: It is. I just wonder, because your comments really resonated with me, because it's not clear to me that you can really do some of those things in acute pain syndromes as you can with chronic pain syndromes. So, therefore, it seemed more measurable in the chronic pain syndromes than in acute.

DR. McGRATH: I see what you mean.

DR. SIMON: So is that correct? I mean, I don't know.

DR. McGRATH: I think, yes, for the complexity of the different variables that -- the complexity of the variables in a chronic pain condition with the patient is suffering the disability, etcetera, I think there are more variables

that are considerable and that, therefore, there is more room for different kinds of criteria to be used in deciding when there has been a meaningful difference, a meaningful improvement.

Yes, but even in the acute pain situation, I don't think it's solely intensity. I think other variables are involved, and so that the same distinction can be made.

CHAIRMAN PETRI: Let me ask again about these concepts of pain half-gone, pain completely gone. Those concepts really weren't in our background reading, and they really haven't been brought out this morning. Let me ask Dr. Hyde, where are they on the list?

DR. HYDE: Well, those are some other things that have been used in studies in the past. These are things -- I mean, partly the question is, you know, what's worked, but they're also the question of what makes sense to you? What is meaningful measurement of an onset or speed of action time to the committee?

So you're putting out things we were familiar with for you to choose from. I mean, one might strike your fancy as being particularly, you know, appropriate to do. Maybe it's difficult, but I

mean, we'd like to know what you think is important.

CHAIRMAN PETRI: Dr. Callahan, did you have a comment?

DR. CALLAHAN: No.

CHAIRMAN PETRI: Dr. Laska.

DR. LASKA: Dr. Leon has some information on this very question, and if he wants to speak, it would be better than my paraphrasing it; but if he doesn't -- As I understand what he has found, it is that in studies where the phrase significant improvement or meaningful improvement have been used, post-inquiry has suggested that patients reach that conclusion that it's significant when their pain is about half-gone.

So it may be we're in the same ballpark.

CHAIRMAN PETRI: Okay. Let me ask about the comment I put down. We were asked by several people, you know, what is meaningful to consumers, what is meaningful to physicians.

I think where the physician comes in is we want durability. I think the patient must as well. So when we get to duration, that was the term I brought up of when the pain relief is wearing off.

So if I could ask Dr. Laska, is that measured in studies? Is that a reliable measure?

DR. LASKA: Maybe Dr. Sunshine wants to comment. Yes, it's done very often. The same technique, the two stopwatches, are used, only the second stopwatch, instead of being used for perceptible pain -- the first one is used for significant or meaningful, the second one for no longer meaningful. That's been very successful as well.

Here again, you say --

CHAIRMAN PETRI: Is the term used, "no longer meaningful"?

DR. LASKA: Dr. Sunshine?

MEMBER OF THE AUDIENCE: We asked them, tell us when your pain has come back to its original level. We don't use just one phrase. The idea is when the medication has stopped working. We try and let the patient make the decision when they no longer -- where they no longer feel the medication is working, and the leads we give them is when it's come back to its original pain or when they feel the treatment is ineffective.

With the long acting drugs, we get meaningful data. There was a question that somebody asked about how long does placebo work. We'll look that up. I mean, we have the data. We just -- I

don't have it in my head, but it is available.

CHAIRMAN PETRI: I think this is a very important comment. I'd like the committee to think about this. In the race to be fast, are we going to shortchange the consumer or the patient, because things are no longer durable?

MEMBER OF THE AUDIENCE: Well, you know, that depends upon the disease entity. In tension headache, you really want to get fast relief, and then the headache is gone, as all of us know, and it's not a problem. That's different with pain of OA or cancer pain or even the pain of third molar extraction. You just don't want it to away. You want it to stay away.

So each disease entity. I don't think there's a differentiation between -- I'm a physician -- or the patient. I think the patient -- the physician speaks for the patient, and the information is the same, should be communicated the same. I don't see the distinction between consumer, patient and physician. The data is important to all three.

CHAIRMAN PETRI: Of course, here we're talking about analgesics. The physician is also a consumer. So, yes, I think that's getting to be the same thing.

Dr. Yocum?

DR. YOCUM: As pertains to the question of pain half-gone, I think we have really kind of defined that trying to put a percentage on it isn't the best. I think meaningful stands. That may be 50 percent to some people. That may be 20 percent to some people. But I don't like the half-gone.

Hearing the discussion, I think meaningful is the most -- is the best one.

CHAIRMAN PETRI: Dr. Liang?

DR. LIANG: Actually, I just thought of this. What are we doing about the young OTC user, you know, the kid? I don't know if they ever know the meaning of meaningful.

CHAIRMAN PETRI: Have kids been studied in these dental pain models? Dr. Max?

DR. MAX: Well, why don't I defer to you, because you do research, Dr. McGrath.

CHAIRMAN PETRI: Dr. McGrath.

DR. McGRATH: I was just going to bring this up. We have been doing studies for a few years on acute post-operative pain, which would, I think, fulfill acute pain model, and it's been an increasing concern in pediatric society; because as surgery moves more in most countries to elective day surgeries and anesthetic techniques involved regional blocks, for

the first time parents rather than health are providers are the ones who have to deal with the child's first breakthrough episode of pain, once they're discharged from the hospital day surgery unit.

Traditionally, parents are told to use whatever OTC products they normally use for themselves, but without any guidelines on how to use those, to tell us they're working and whether they need to switch to a different product if they're not or if the dose was inaccurate.

So I think this is a big issue, and I was going to use that as an example as a means of saying that I think we can't lose sight of the duration of meaningful pain reduction, and that children can make those distinctions about feeling better, and parents can help their children to administer OTC products, I think, very safely and very effectively; but at the present time, there are not good guidelines.

I think that needs to be forthcoming and not simply be centralized to areas that happen to have a pediatric pain clinic where they're putting that information into their community.

DR. LIANG: In rheumatoid arthritis, I think part of our dogma is that kids don't complain of pain.

CHAIRMAN PETRI: They stop moving.

DR. LIANG: They stop moving or they limp, but they don't say pain. So is that true with other painful states in children or is it known?

DR. McGRATH: I haven't worked with as many children with juvenile rheumatoid arthritis. Certainly, the ones that are referred to our pain clinic for pain management are able to tell us what hurts, how it hurts, and which interventions are working better.

So I believe that children have the capability to do that. How widespread, I really can't comment on that.

DR. MAX: With regard to having -- I think there was a question --

CHAIRMAN PETRI: This is Dr. Max speaking.

DR. MAX: Dr. Max. Is there methodology that children can use to show onset. I believe that down to what is about five or six years old, kids can reliable record pain on a category scale. When you get down to five or six, sometimes it's people use faces, five categories of happy or sad faces or various other categories, but one can just give them a scale every 15 minutes or every 10 minutes, and then use the survival analysis methods to calculate onset.

The question of whether -- I have not seen published studies where children used a stopwatch to indicate meaningful relief or another criterion, but that's not a necessary piece of using the onset methodology that Gene is talking about.

CHAIRMAN PETRI: Now let me summarize where we are at this point. We've sort of whittled down the list of concepts, and we're left with "meaningful relief" and then "pain came back to original level."

Any dissension at this point? Any other comments on sort of whittling down what we thought were the important points? Dr. Blewitt first.

DR. BLEWITT: Well, I just had one comment. That is, as you go through these parameters, what you're really defining is onset, and not necessarily fast. Again, I think these are two different concepts.

These are the parameters to measure onset of pain relief. Whether that equates with fast or not, you really don't know. So to determine what fast is, I think fast is a qualitative term. I think it deserves a different kind of a look.

CHAIRMAN PETRI: We haven't even gotten to fast. All I'm doing right now is just making sure we

all have a consensus on the concept.

DR. BLEWITT: Well, the question relates to --

CHAIRMAN PETRI: Yes. No, we have --

DR. BLEWITT: -- should fast be measured.

CHAIRMAN PETRI: Yes. We have not finished with question 2. I think there was a comment from the audience.

MEMBER OF THE AUDIENCE: I'm Bill Beaver from Georgetown. In relation to the duration that you were talking about, the duration of effect, that's usually -- It's usually not measured with a stopwatch, and the current method that's most commonly used is for the patient to tell you when the medication is no longer working, their pain has returned, and they want -- they feel it's appropriate to take a back-up medication.

All of these studies we do, of course, have the option of taking a back-up medication, and this has turned out to be a very good index of duration. We've used it in very long acting NSAIDs, things like diflunisal and so on. You can use it in short acting NSAIDs.

Furthermore, it is clinically very relevant, because in fact, that is the judgment that

a patient would make, particularly in an outpatient situation or in an OTC situation. They're the ones that decide, hey, this stuff worked pretty well, but it sort of pooped out, and now I need something more. It's that time interval that's usually used as the measure of duration.

CHAIRMAN PETRI: Now this could be measured with a stopwatch technique.

MEMBER OF THE AUDIENCE: The problem is how many stopwatches do you want in play at one time, and you get -- particularly, if you're looking at outpatient models, you get into people getting confused; whereas, if you have on the patient report that they're filling out how bad is your pain at these different points, the point at which they say my pain relief has gone or my pain is now moderate or severe again, I want to remedicate, and they indicate the time at which they've taken the remedication, but it's not generally done with yet another stopwatch for mainly practical reasons, unless you want to do it investigationally on an inpatient basis.

CHAIRMAN PETRI: Dr. Laska.

DR. LASKA: I think Dr. Sunshine is the counter example of that. There are people who have used stopwatches to --

MEMBER OF THE AUDIENCE: Oh, it has been used as a research tool, but most of the regular analgesic studies we're are doing, that stopwatch for duration is not a part of those studies.

DR. LASKA: I think the important point is that duration of offset is an easier thing to measure for many reasons. Calling the patient's attention or the consumer's attention to tell me when the pain is gone is a vastly different enterprise to the one that's obvious. It's back again; here it is; I need some help.

So you can walk over to your watch and look at when that happens; whereas, with the stopwatch there's a psychological dimension as well. You better pay attention, you may not notice when the pain goes away.

So there's a rationale for Dr. Beaver's comments that the stopwatch itself may not be necessary. I just want to caution, though, that a discussion about offset may not be as easily paralleled as onset, because the analysis issues become equally large.

Just one simple example: Most people analyze the time of offset and include all subjects in trial as if they were all equivalent patients, but

there's a vast difference between a patient who remedicates within the first half an hour or 45 minutes or an hour, because they failed to get relief, from a patient who gets relief for four hours and then remedicates.

Putting them altogether answers two different questions. Putting them together answers a mixed question, one that says let's talk about offset for those patients who have gotten effect makes sense. Mixing them is complex. I don't think that's the task of the committee, and we should not make the mistake of thinking they're the trivial issues.

CHAIRMAN PETRI: Now I'd like to combine part of question 2 now with question 1. This is getting to Dr. Blewitt's point. Should fast be measured clinically?

So I'd like to go around and have people give their comments on whether it should be measured, but then I'm also going to ask you to tell us how. Dr. Blewitt, if you could start, and we'll go around.

DR. BLEWITT: Well, it's a tough question, obviously, or we wouldn't be here. But my -- Again, my issue is trying to measure qualitative terms by quantitative methods.

I imagine that there are perhaps market

research methods to determine what people feel is fast or not. I don't know that there is a clinical methodology that relates to fast.

Now there are ways in which that you can demonstrate that one product is faster than another. So it then becomes a relative issue, comparative issue, and that takes you into another dimension, I think. But in terms of defining fast, I think that it's such an abstract term and a term of art that I think it's hard to put any particular value on it. I think it would be very difficult.

CHAIRMAN PETRI: Dr. Laska.

DR. LASKA: I think where the same conundrum often happens with edge effects. I think it's very clear when something is not fast, and when something is really fast, that's also clear; but where you would put a break point to talk about middle range is difficult.

Wherever you put it, a particular drug whose median time is a minute beyond that will have a legitimate cry that you left me out by a minute. I'm not as fast as that or I'm faster. I'm not fast, because I'm off by a minute.

I think using a word to characterize a quantitative event is a bit tricky and difficult and

maybe not worth doing. But I do think providing information on speed of onset, on rapidity of onset, however defined, does make sense, and that's where my vote goes.

CHAIRMAN PETRI: We don't have to use the word fast. Obviously, we can substitute numbers. Dr. Max.

DR. MAX: I don't think that fast in isolation should be a criterion that the FDA should get into, for the reasons that I said, that if you define -- that it's easy to manipulate a clinical trial to minimize the amount of pain and make the onset faster or maximize the placebo effect, leading to very poor scientific quality trials that are only conducted for this purpose. However, if the FDA can think of a way that's practical to set some comparison between the drug that's being put forth and some comparator, that can be very scientifically meaningful, but I think you're going to ask this again about faster. Right?

CHAIRMAN PETRI: We have to start with fast. Dr. Moreland.

DR. MORELAND: I would agree with the comments that have just been made there. Obviously, this is a new realm for me, and I don't have a lot to

add to these models that have been put forth, but I would favor that we leave it in the terms of what's meaningful to the patient and then in the terms of they receive meaningful relief within so many minutes, and define it in those broad terms.

CHAIRMAN PETRI: Ms. Malone, if I could ask you to direct your comments both to what you think the consumer would need, but also address this idea of how should we define or measure fast; for example, time in minutes, a set period of time.

MS. MALONE: I don't think -- I like the idea of a range more than a specific number, because there are so many variables. I think the consumer has a right to some expectation of when the medication should be working, be it a half-hour or an hour, so that they don't redose or overmedicate too soon.

I mean, they need to know that, well, this should be kicking in in about a half-hour. If it doesn't, then, you know, I better take some more or go on to something else.

Again, what concerns me is in advertising. They're going to want to use these catch words, because that's what grabs the people to go and get these medications. So they will want to use fast or quicker.

I'm always amused, because I've become very discerning now, and when I hear the advertising and they will say it's faster, and you go faster than what; and they don't always tell you that, you know.

CHAIRMAN PETRI: For example, we're all confused by the H2 blockers being advertised on television. We don't want that same disaster with our analgesics. Dr. Liang.

DR. LIANG: I would like to make this question go away. What I would suggest --

CHAIRMAN PETRI: Because Dr. Liang is getting a headache?

DR. LIANG: Seriously, I would, for instance, make it a requirement that all OTC analgesics work within 30 minutes or some face valid number, and force everyone to put fast in their labeling. But if you want to do it the hard way -- I think the key is -- I don't believe in patronizing consumers, because I'm one, and I like to see the numbers not reduced and a range and a standard assay as a minimum, not as a maximum.

CHAIRMAN PETRI: Dr. Tilley.

DR. TILLEY: Well, I, as you know, being a statistician, would prefer the more quantitative approach to this problem. The other thing that

concerns me is that fast -- I think the definition of fast is changing over time, and that it would require continuous sampling of consumer panels.

For example, if you look at our aging population, they're much more active now than they were, you know, a few years ago, and I think that's going to continue. The activity level is going to continue to increase. As people are more active, then pain may become more of an issue, especially in the kind of diseases that we're talking about.

So what was fast ten years ago to people with osteoarthritis may not be fast anymore, because there's other things that are happening for them. So I think that fast by its qualitative nature is very difficult.

I don't think either that we put even any one quantitative measure that would really define fast for us here today. So I'm --

CHAIRMAN PETRI: Let me pin you down, though. So we have these choices, time in minutes or a set period of time, for example, Dr. Liang's 30 minutes. What do you think is fast from a statistical point of view?

DR. TILLEY: Okay. What I would like to see -- and speaking both as a consumer and a

statistician -- would be some idea of how many people responded -- like of the people that had my kind of disease, what proportion responded to this drug, maybe some range on those proportions if there were multiple studies, and then I'd like to know, of those people who responded, what was the range on the response times, and what was the -- you know, 50 -- I would like to know if 50 -- I could certainly understand 50 percent of the people experienced meaningful relief in X period of time, but it would also be real important to me to know that, of everybody who took this, only ten percent got any relief at all.

So, you know, that's where I'm struggling with the one word fast.

CHAIRMAN PETRI: Dr. Simon.

DR. SIMON: I'd like not to pander to the commercial interests, and I think that fast is only doing so. I think that what Dr. Tilley just described would be a much better way for me as a physician to interpret the data, and I believe that consumers, if it is illustrative and understandable because it's presented appropriately, will also appreciate that kind of data more so than any kind of construct that would pejoratively describe something as fast.

CHAIRMAN PETRI: Dr. Fernandez-Madrid.

DR. FERNANDEZ-MADRID: I also support that. I think the integration of the onset, the time of onset that we discussed of the product that has with a meaningful response as suggested by Dr. Tilley is appropriate.

I think that one should draw the line in terms to call a drug fast, and I also like a minimum time of response, and this allowed the claim of faster.

CHAIRMAN PETRI: Dr. McGrath.

DR. McGRATH: I would simply support the previous speakers' comments. I don't think fast can be measured clinically for the reasons they outlined, and that we have to differentiate qualitative from quantitative. I would really move and support anything that we can do to help labeling be more realistic in terms of quantitative effects and so on, and not what fast or faster means.

CHAIRMAN PETRI: Dr. Yocum.

DR. YOCUM: Well, I guess I support the previous speakers. I think in the prescription area the studies can speak for themselves, because they are defined areas, and they are defined diseases that they're going for approval.

In the OTC, though, again, I guess,

setting standards and so on and so forth and definitions -- As you say, we're talking about analgesics. Now we're talking about H2 blockers. We can have a whole lot of meetings deciding what is fast or not, and I think the decision is whether just to disallow it, period. But, you know, in the OTC market the consumer usually decides.

As Leona said, the ones that don't work, they find out relatively quick, and they don't go back and buy it again. So is that actually a faster way to decide this or are we going to try to set standards?

I think, in the OTC market the consumer decides. Okay, so he or she bought a bottle of pills that isn't going to help them, but they aren't going to buy those pills again relatively quickly.

CHAIRMAN PETRI: Now let me challenge you on that. Why should we allow the consumer to waste his or her money that first go-round if we could provide them with a number?

DR. YOCUM: Because I don't think whatever we do here is going to stop that consumer from trying it, and I think that we're kidding ourselves if we think we're going to do that.

CHAIRMAN PETRI: Dr. Pucino.

DR. PUCINO: I agree with the other

members in that it should be a period of time effect and also it should be disease specific, and it should be consumer meaningful response.

CHAIRMAN PETRI: Dr. Koda-Kimble.

DR. KODA-KIMBLE: I really have nothing to add to the other speakers. I support what has been said.

CHAIRMAN PETRI: Dr. Callahan.

DR. CALLAHAN: I agree with the other speakers, and I particularly support Dr. Tilley's point of putting what percentage of people respond, because I would be very interested if something -- if only five percent of people respond to something, even if they respond very quickly.

CHAIRMAN PETRI: Dr. Tong.

DR. TONG: I don't have any profound addition to what's already been said here. It's not possible to disallow the use of the word fast on over-the-counter labels and advertising. I believe, as consumers, that we're able to make a judgment call.

I'd like to see the idea of time and disease specific details if, you know, that's the role of the agency to require makers of these companies in order to make statements like fast, that they need to show it; but I'm worried that it will be coopted into

a promotional and advertising aspect, but that's not our role here to discuss that.

CHAIRMAN PETRI: Dr. McKinley-Grant.

DR. McKINLEY-GRANT: Actually, I agree with the rest of the panel, though it actually also occurred to me that the word fast probably has somewhat of a placebo effect for the consumer and enhances the effects of the medications when they're taking it. But I think the comments about the meaningful relief are important, and would think that we should, in the consumer readout, give information about the different diseases; and if there is some way we could do a sampling to determine what to the consumer fast means, I think that would be helpful.

CHAIRMAN PETRI: Dr. Brandt.

DR. BRANDT: Yeah, I think, certainly, data is always good, but I would like to ask a question that perhaps Ms. Malone might address, and it has to do with disease specificity, and labels are finite in length, and there are a lot of diseases that are associated with pain.

If a consumer has information on data with regard to the effectiveness of a pill for migraine headache and you have rheumatoid arthritis pain, how much does that count?

MS. MALONE: Well, I think normally word gets around, you know, amongst consumers who have various ailments as to, you know, what worked with them and why don't you try this for this. I know I think it was Excedrin that was approved for migraine use recently, and on the label, I mean, was the exact -- If I'm correct, it was the exact same formula, but because it was new for migraine use, you know, in advertising they have this printed on the label.

So that did bring it to the attention of people. I'm not sure that I answered you. Again, someone has to tell them that you can use it for something or why would they try it?

CHAIRMAN PETRI: To summarize where we are at this point, I think the panel is in agreement that we don't want to use the word fast, that we prefer a number; but I'm not sure that we really addressed question 1 that asks us to choose between giving a median time in minutes or a set period of time.

Now it's a given, we all agree we want to know the percent responders first, and we want the consumer and the patient to know that, but if that's a given, I'd like the panel to reapply themselves to this issue.

Should we give the median time in minutes

or recommend that that be done, or is it better to give a set period of time which might get this idea that there is a range, a confidence interval, around that median? Comments? Dr. Laska.

DR. LASKA: Thank you. I think the issue of giving a set period of time is the equivalent of the concept of fast. If you say it works within 30 minutes, you're saying --

CHAIRMAN PETRI: Yes, we are, but we're not using that word fast.

DR. LASKA: I agree.

CHAIRMAN PETRI: We're giving a number.

DR. LASKA: I agree, but -- Well, giving a number, meaning that the median -- but the number is the barrier, because the median is below some barrier. We're willing to say it falls in this range.

CHAIRMAN PETRI: Well, I think we have a choice. We can give that number. We can say blank percent respond to this drug, and the median time to meaningful relief is 45 minutes; or we can say it's within the range 30 minutes to 60 minutes.

DR. LASKA: Right. I think the proposal that under -- well, the analysis that underpins this so called conditional approach really expects you to respond by saying what the parameter value estimates

are, rather than saying there is an arbitrary period with which we would like to know does it fall to the left of that period.

So my vote should be that the analysis, the actual numbers found be characterized, and that would be in a range, but the range is data driven. So if there were ten studies and the onset time for those people who responded was between, in one study, half an hour and the rest up to an hour, one could say the median response time was within a half an hour to an hour, and the proportion of the patients who responded was whatever it is.

If you were to set as a committee a range, that would be equivalent to saying fast means you have onset in less than half an hour. So I think that the committee has almost, by definition, spoken against the notion of us defining a range.

CHAIRMAN PETRI: I agree. I don't think the committee wants to define fast, because it's going to be different for each disease, but I think the committee is in favor of giving a number based on data.

DR. LASKA: Two numbers, one the proportion responding. The second is something about median time, and you probably have to give a range for

that median time, data driven.

CHAIRMAN PETRI: Obviously, I think it's more accurate to give that range than to give one median number, but I think there are lots of comments now. Dr. Max.

DR. MAX: I would support that by suggesting that there be a table in the labeling information with all the different studies and for each, the proportion who responded and the 25-75 percent range of how fast they responded, so people can just look and see when they need to respond.

I oppose compressing this down to make it into a competitive claims something on the box covers or something in the ads.

CHAIRMAN PETRI: I think, though, that we need to have some summary. I mean, we could have a label where you need your microscope to read through all the studies. Let me ask Ms. Malone. Is a summary statement or a list of all studies going to be most appropriate for the consumer and/or the patient?

MS. MALONE: There are those that will read the entire insert and find minute problems, but I think most people want to look and see how many people with what I have got relief, you know, and when did it come. What should I be looking for.

CHAIRMAN PETRI: Dr. Koda-Kimble.

DR. KODA-KIMBLE: It seems to me -- I mean, at least in the OTC group, we look at an ingredient, but we don't look at formulation. I mean, now you're talking -- Let's talk about a liquid versus a suspensial versus enteric coat that doesn't dissolve, all of those sorts of things.

I'm really struggling with this in terms of even putting the kind of information we're asking for the consumer as a list. There's so many, many variables here, and it seems to me, if only ten percent, for example, respond within 30-45 minutes for a particular condition, it's up to the advisory panel, whichever that panel is, to say we don't consider that particularly efficacious.

So it seems to me, there's a definition that has to go into -- Part of this has to be considered within what we consider efficacious, and what the consumer can reasonably expect.

CHAIRMAN PETRI: I think we have stated that we really want to see that number, that percent that respond. Then the other information is conditional upon that. Of those who respond, what is the median time for meaningful relief. Do you feel uncomfortable with that?

DR. KODA-KIMBLE: Well, as I said, when I'm feeling a little uncomfortable now is now we're talking about product. When you talk about product, you're not just talking about ingredient. You're talking about combination of ingredient. You're talking about formulation. You're talking about pharmacokinetics, pharmacodynamics. What is the probability that this ingredient will get into the system.

Basically, I'm going back to what Nick Holder said at the very beginning. So it begins to be so complex that, if we put the data down, I don't know what we're referring to. You know, we're collapsing this data, and I don't know what we're talking about.

CHAIRMAN PETRI: Well, I don't think that it can be collapsed. It has to be the data for that particular formulation, but let me ask -- Dr. Katz wanted to respond to that.

DR. KATZ: I agree with the comment that was just made. One needs to -- In a sense, part of the discussion that we're having today is also for both prescription and OTC products. For a prescription product, it's easier logistically to have a section on the label to describe what the studies say, what the results are, and to go from there.

OTC products -- Most of the OTC products that are out there are ingredients. They're not specific products, unless those products happen to be switched and are NDA products. So that you may not have all of that information that you're now describing available.

Then there's an additional logistic problem of where are you going to put it, because you can't put it on the carton. It won't fit. So you're -- Not all products are required that are OTC as well to have patient information or a patient brochure.

So that, if you're going to again ask for that information to be contained somewhere, if you're expecting that it will be in a patient brochure or patient information packaging, you'll have to remember that not all products will have that, and they're not required to have that. It's voluntary.

So there's going to be some products that will have it, some products that won't have it, some products that may have that information because again they were originally an NDA type of a switch product that would have specific product studies that were done. Others then are going to just be ingredients that we've approved via the monograph.

So there are other things that one could

consider which would be in a patient brochure to have a section of expectation of benefit, which may be able to address some of these issues; but it's really not going to address all of the concerns that people are raising about how to describe either the onset or the appreciable or meaningful relief.

I'm not sure where I'm expecting that from this discussion where people are planning to have it go.

CHAIRMAN PETRI: Dr. Soller.

DR. SOLLER: Yes. I just had a -- Soller, NDMA. I just had a brief comment here, following up on what Dr. Katz was saying.

Having spent a long time with OTC labeling, I find it difficult to think about the kind of labeling that might say something along the lines that 50 percent can expect meaningful relief in 10-20 minutes for mild headache -- I mean, if we want to be accurate -- and we have another percentage maybe for severe headache, or even if we're not going to even do intensity, we start thinking about headache, dysmenorrhea, aches and pains of cold.

Maybe trials come out and we find aches and pains of cold are different than muscular skeletal. You have other concurrent conditions with

colds. And now the list gets very long.

I'll just take a parenthetical sidestep. I will tell you from what we're doing on the proposed labeling reformatting for OTCs that what has been proposed by FDA won't fit 50 percent of our labels right now in terms of the new reformatting.

So you start adding this into one of the most complex labeling categories, analgesics and cough-cold combinations, and there is a tremendous crunch that just won't work.

So I come out with two other points. Even if you were to try and do this in a more de minimis way where you're really devolving the science down to a very general term to say something like a majority can expect meaningful relief in 10-15 minutes, and you start doing the individual indications, I'm not sure that a consumer wouldn't think, well, I'm usually not in the majority of things, I'm going to double up.

Another thing, I may have come from a very different school, but I don't know why we would sit with the kind of phrase that would say a majority could expect. When we do that, we are potentially taking away the optimism of relief from a person approaching that particular product.

So I think in this situation, while onset

and magnitude effect, Mike, as you were referring to it before, may be very important from a drug approval standpoint, how that gets translated down to a consumer, I don't think, is necessarily a statistical issue when you get there.

I think less is more in this situation, and when you say fast pain relief, the consumer knows that that's a qualitative term applying to products used for acute conditions, and they're using these products today very effectively, very safely, and to their satisfaction.

CHAIRMAN PETRI: Dr. Yocum.

DR. YOCUM: I agree with those statements. Again, regulating fast just -- We're going to start regulating fast and everything, and I was sitting here trying to imagine what the back of the box is going to look like that the patients are trying to read, and it just didn't -- I mean, to me, even in nonsteroidal anti-inflammatory drugs in the clinic, when I prescribe one for a patient, I realize that it is effective in 60 percent of patients, and the patient may well come back two weeks later and have no effect. Then I'm going to go on to the next thing.

So there is trial and error by myself, like the consumer. So the consumer is doing trial and

error. What I guess we seem to be bypassing here is -- so now we're going to take up the whole back of the box defining fast with that particular compound. What I am actually more interested is the safety of that compound. Now where is that going to go, and what is it actually going to do to the patient?

Is the safety of that compound more important or how fast it works? I guess I would rather attune myself to safety and let the consumer decide fast, because I still as a physician am doing trial and error in fast.

CHAIRMAN PETRI: Well, I'm not sure what you were agreeing with. We're sort of coming full circle. Let me go back to Ms. Malone. Is it important for the consumer and the patient to know if the onset of meaningful pain relief is significantly different for one product than another for the same disease?

MS. MALONE: I think so. It should be noted anyway.

CHAIRMAN PETRI: Obviously, the consumer and the patient care about safety, too.

MS. MALONE: Right.

CHAIRMAN PETRI: But the reason we got into this can of worms was it is still important to

know.

DR. YOCUM: But I go back to Dr. Max's comments. Yocum again, I'm sorry. That is, that if we define this as effective in a headache, Dr. Max pointed out that they'll go get some -- a group of people with -- consumers with a headache that is ten percent of the maximum headache and use that group of headache to then redefine the onset.

You talked about a baby tooth coming out and the tooth extraction, of how you define it. So how we define a headache. Then we're going to move to the intensity of the headache that was relieved 50 percent in so many people. It becomes a bottomless pit. I don't think I'm going in circles.

CHAIRMAN PETRI: Well, we haven't even gotten to the question about recommended study design. So for the moment, let's table how study designs can be manipulated. Dr. Laska.

DR. LASKA: I think Dr. Yocum's view that the patient does experimentation and he does experimentation is probably an accurate reflection of what takes place, but you will admit, I hope, that it's a very inefficient way to do business. Large studies are a better way to find out about probabilities of effects, and the magnitude of those

effects.

So I think this business of getting information from large clinical trials which tells you that will allow you and the individual consumer to make a judgment in a more informed way.

Mitchell's point about manipulating the system is correct, but it's not correct. In that sense, every clinical trial has that potential danger. IF you want to show effect sizes are greater and you want to show differences or no differences, you pick a population to demonstrate what you would like to do.

That game is widely understood and appreciated by, certainly, the regulatory authorities and the experts in the field. So while it is possible, it is not something that anybody gets away with.

I don't think you can really say I'm going to manipulate my trials to show better onset by picking the population of the study, because it will come out in the wash.

CHAIRMAN PETRI: Dr. Simon.

DR. SIMON: I have actually gone full circle through this discussion. I now am totally convinced that I would prefer not to get involved in a discussion of whether or not I want to buy a Lincoln

Continental or a Chevrolet when I go in and look at a consumer product, and I don't think the FDA or this committee should be involved in trying to apply these appellations to these products, and I'm even -- I'm staying away from fast.

I think that the question is --

CHAIRMAN PETRI: But, Lee, you would want to know maybe miles per gallon or something. Right?

DR. SIMON: No. No. I actually don't -- I'm not convinced that, other than defining its efficacy, whatever that bar will be -- and I think we can define that and that the consumers can help us define that also. Other than that, I'm not entirely sure that we should be regulating that market environment. The consumer will. They will either buy it or not.

CHAIRMAN PETRI: Well, let me challenge you, because we did discuss this. Isn't time to meaningful pain relief part of efficacy?

DR. SIMON: As I said, yes, it is, but I'm still really skeptical about the technology. I think it's great to see these diagrams. I think it's very interesting to sit here and think about this as a theoretic possibility.

I'm challenged by the issue of expressing

the data in a cogent, reasonable way for somebody to read on a box. I am overwhelmed myself as someone who theoretically is supposed to know something about this by the nuances of the interpretation.

I think that consumers are very smart. I don't think they can actually see the nuances, because they're not going to hear this entire discussion every time they go in to buy an over-the-counter Ibuprofen.

So I'm absolutely now convinced that we should get out of this business, set a bar, and let them advertise all they want; and as long as they're not saying a lie, let them go ahead and do that and not get into the regulatory environment.

CHAIRMAN PETRI: No, but -- Let me remind you again about those H2 blocker ads.

DR. SIMON: No, no, no. I disagree with you about that. I again will say that I believe we should know that they're safe. I think that it has to be proven and clearly studied. I think we should set a bar for what responsiveness should mean, but if they're going to claim they are ten seconds faster in response, I don't think it's measurable in this context, and I don't think we should get involved in the regulatory.

CHAIRMAN PETRI: We haven't even gotten to

faster,. Dr. Max.

DR. MAX: I guess my understanding is that, if the government doesn't take a position on -- and now we're talking about faster -- there are a lot of companies in this room that are trying to make faster analgesics, and it will just be left to the courts.

So they will come out with a claim saying our drug that is five minutes faster in onset than another drug, and there wills be law suits in court battles, and an issue is should the government, FDA or FTC, get into this and try to regulate, or should we leave it to the courts.

You know, I think it sounds like that's one of the main practical issues that's going to come up.

CHAIRMAN PETRI: Let me ask Dr. Weintraub to comment a little bit on the recent discussion.

DR. WEINTRAUB: First of all, I think we have to remember that we frequently approve drugs, and this is total approval for many pain problems, that we don't even know what the consumer is using it for in the OTC market, but we hope they're doing it correctly, and we think in general they're doing a good job.

We take dental extraction pain. We take -- you know, and that will be one of our main -- That will allow a manufacturer to make a very important claim, a general pain claim, and it's based on just one type of pain model.

Also, we are -- We have established different models for at least three -- We have at least three different models. This was in your packet. We have the general pain claim. We have the menstrual cramps, and we have headache, because we see that there are differences in those types of pain.

So many of the things that Dr. Soller said are not -- you know, didn't really apply to this discussion; but what he did say and was very correct is that it's going to be very difficult to take this term of art and make it into a regulatory term.

Are we trying to do that? I don't think so. I really don't think so. We are trying to understand how consumers, physicians, patients, all mixed together can get an understanding of how fast their drug starts to work, the speed of onset.

The reason we're doing it is because we are facing it in every field that we can say. You name a field. Today I heard from our advertising people after the morning session at the break that

people are talking about anti-hypertensive drugs and speed of onset. An anti-hypertensive drug is a drug you take for a long time, hopefully, for many, many years and take it regularly.

So what does the speed of onset mean? It doesn't mean much. Right? And there's going to be advertising on that. So we can't yet throw it away and say, okay, you guys, you guys deal with that, our hands are clean. We're pure; we're purer than pure, and we don't even know that that's going on.

We can't do that. We've got to get into the trenches, into mud up to our eyeballs, and deal with this issue. So -- Now one thing that Dr. Simon said -- maybe that will be the best approach.

By the way, I'm taking very careful notes. We're having this meeting transcribed, and we're going to think about this, and everybody is going to think about it. It's going to be discussed over and over again in the FDA.

Dr. Simon says make a bar; say, okay, 30 minutes, that's it. We'll at least get our hands dirty or the tips of our fingers dirty. Won't get up to mud to our eyeballs; we'll get the tips of our fingers dirty, and we'll say that's it.

That's perfectly -- Maybe that's the best

way, but we've got to decide, and we love the discussion that's going on here, because it's you and him, fight, and we don't fight with you. No, we're actually --

CHAIRMAN PETRI: You're going to pick up the pieces.

DR. WEINTRAUB: That's right. That's right.

CHAIRMAN PETRI: Dr. Koda-Kimble had a comment.

DR. KODA-KIMBLE: I'm thinking -- Michael, if we said, for example -- It's very hard to separate this discussion, because you're asking us to look at fast from a very broad perspective, whether that's prescription drugs or -- and we're focused in on analgesics, and I'm focused in on OTC analgesics.

Presuming the bar was set for -- and I'm thinking about a drug that makes a claim for acute -- relief of acute pain versus chronic pain, and I don't know that we have this distinction even within the OTC class. I mean, is that -- I mean, one of the things -- Is that possible?

DR. WEINTRAUB: No, we don't have that distinction in the OTC class.

DR. KODA-KIMBLE: But there are drugs in

the OTC class, and there are probably products in the OTC class that have an onset because of either their formulation or the nature of the drug itself that have an onset of, let's say, two hours, which according to the discussion at least in this room would not be considered fast.

DR. WEINTRAUB: That's right. I remember one of the discussions we had where Dr. Katz raised the point, look, saying that all OTC drugs have to be relatively fast. They have to take effect in a reasonable period of time, as we heard this morning.

We talked about what was a reasonable period of time, but we don't have a definition for chronic pain in OTC drugs.

CHAIRMAN PETRI: I want to bring everybody back now to the first question. I realize -- We've got to get somewhere. We got to the point where we thought that a range was a better way to express the onset of meaningful pain relief than just giving one number, and then Dr. Simon brought up, well, let's throw that out, let's have our bar 30 minutes.

I'd just like to get a feeling of how the committee is splitting on this one thing. Dr. Tilley.

DR. TILLEY: I guess I'm hearing some diversity of opinion, and some of it, I think, is

getting driven -- is being driven by -- You asked us what we want. Now what we want and what's practical may be two different things.

You know, those are not the same. You heard what we want. Okay? Now if that's not possible -- I mean, it certainly would be possible to pick -- if dental pain is the standard on which pain drugs are tested, you could certainly, you know, some kind of descriptive information about dental pain.

If we move to a bar, we are just substituting the bar number for fast, and that bar, as I said before, I think, is relative to the time, to all sorts of things.

So -- and I mean, there's also no reason that that word fast has to be used at all. I mean, if it's too difficult to define, rather than throwing up your hands and saying I cannot define fast, so I have to just use the word fast -- I mean, the other option is don't use the word at all.

CHAIRMAN PETRI: Well, let's redefine this in terms of what we want. So let me again ask for the committee's feeling on whether we want a range for the onset of meaningful pain relief or we want Lee Simon's approach, a bar. Dr. Callahan.

DR. CALLAHAN: I just want to clarify.

Are we determining what we want in terms of what can be used for advertising, not what is mandated to be on every single label?

CHAIRMAN PETRI: Let's not get to how it's going to be used. Let's think about what does the consumer and the patient benefit from knowing and, of course, the physician, if it's a prescription analgesic.

DR. CALLAHAN: So this could just have to be known in any range of ways? I mean, some of the discussion afterwards almost sounded like, when we were making the other comments is the fear was that everybody would have to put all of that information on every single product, and that's why -- I'm trying to clarify. Do we want to --

CHAIRMAN PETRI: I think that's a separate issue. Let's try to just sort of stick to something where we can reach, hopefully, a consensus. Is that useful information to have for the physician, the patient, the consumer, the range for the onset of meaningful pain relief, or is it not useful and all we really need to tell the consumer and the patient is does that product meet that bar?

DR. SIMON: That's not fair, because that's not accurate.

CHAIRMAN PETRI: Well, that's why I said that I have a subordinate clause here. Is this what we want?

DR. SIMON: You see, that's the problem, because we're really not here to discuss to the exclusion of reality what we want. We're here to discuss the practicality of having to interpret this for the consumer, and then how it can actually be applied. Unfortunately, what we want can't be.

CHAIRMAN PETRI: Well, I think for some of the pain models we could get this. So let me again ask Dr. Max and Dr. Laska. Isn't it possible within the dental pain model to give a range for the onset of meaningful pain relief? Would that be useful information for dentists to have?

DR. MAX; I think it would generally be useful for anyone if it's a comparative number between products, but for the reasons that I indicated, if it's just for one product alone, it wouldn't be very meaningful, because people could manipulate the model.

CHAIRMAN PETRI: Dr. Laska.

DR. LASKA: I don't agree. I think the manipulation issue is the same in any -- whether it's efficacy comparisons or onset comparisons. I think you don't need a comparison to make the point that in

ten studies these are the proportions we found, and these are the distributions of time to onset, and I think you can summarize that in two or three numbers.

CHAIRMAN PETRI: So we have disagreement. Ms. Malone.

MS. MALONE: I think that the consumer needs to know what expectations to have of this drug, when it will start to work.

CHAIRMAN PETRI: Do you think Dr. Simon's comment about a bar, let's say 30 minutes -- is that acceptable? Does the consumer need or want to know more?

MS. MALONE: Well, as long as it's stated. If it's stated that within 30 minutes the average user will find relief or begin to get relief, get optimum relief, whatever the expectation is, you know, it has to be stated; because why would they take this drug?

CHAIRMAN PETRI: Now it's hard for me to phrase a question, but let me try again. We have a choice. We can give a range. We're going to just take the dental pain model now, with a realization that the methodologies may not be there for any of the other pain models or diseases.

Is it the choice of each committee member to go for a range of onset of meaningful pain relief

or is it the choice of the committee members to go for that bar?

I'd like to just go around and ask everyone to choose. Dr. Blewitt.

DR. BLEWITT: I'd actually like to ask a question of the consultants, if I may, with regard to the onset of pain relief with existing marketed analgesics. Let's just take the spectrum of aspirin, acetaminophen and ibuprofen and so forth -- and whether there are noteworthy differences in the onset of meaningful relief with those drugs, the point being isn't the universe as -- the existing OTC universe known today, and are we adding to that knowledge by providing this kind of information?

Seems to me that most of these are fairly similar in terms of their behavior.

CHAIRMAN PETRI: But isn't the question that the newer formulations may not behave the same way? So I think, you know, we're asking this question not just for today, but for tomorrow's products.

DR. BLEWITT: Well, but you see, where that takes you then is to the faster part of this. It doesn't take you to the fast part, the standard part of it. It only then relates to how does it compare with the existing analgesics.

So what I'm suggesting is that by providing this kind of quantitative data in the existing marketplace, you're not really adding to the information base. We know how these things work, and it then remains for any company with a new formulation or a new molecular entity or whatever who wants to demonstrate that they are faster or try to attempt to do that, that then becomes a very different situation.

CHAIRMAN PETRI: We haven't even gotten --

DR. BLEWITT: I'm really differentiating between the term fast and faster.

CHAIRMAN PETRI: We haven't gotten to faster. But let me ask you to come back to the question that's on the table. Which do you prefer, to know the range or to have a bar? Dr. Blewitt, can you pick between those two?

DR. BLEWITT: I'll abstain.

CHAIRMAN PETRI: I didn't know that was a choice. Dr. Laska.

DR. LASKA: In response to Dr. Blewitt, I challenge him to tell us what it is that he thinks the time to meaningful onset is for these over-the-counter drugs. I think you may know from some studies, but as a general principle it's not quite enough.

I would argue that information out would

be adding to the knowledge base of consumers as well as physicians. On the vote for you --

CHAIRMAN PETRI: Range or bar?

DR. LASKA: Yes. On the vote for your question, I think bar gets us back to the equivalent of fast. So it has to be, in my judgment, a range of onset time.

CHAIRMAN PETRI: Dr. Max.

DR. MAX: I think it's well known that between study comparisons of one drug to another are subject to wild swings --

CHAIRMAN PETRI: Don't worry about faster. We'll get to that.

DR. MAX: Well, okay. I'm agin all -- anything except for comparative claims. I'm agin getting into fast except for some detailed information in the body of the label that somebody can dig for, but I don't want anything about fast noncomparative on the box where it could be used for --

CHAIRMAN PETRI: Again, I'm not asking about fast or faster. If you have a choice between knowing the range or having the bar, what would you prefer?

DR. MAX: I would want the actual number for --

CHAIRMAN PETRI: Then the range.

DR. MAX: Okay, a range, 25 percent, 75 percent, for onset -- time of onset.

CHAIRMAN PETRI: I see. You won't be able to talk about faster unless you have that range. Dr. Moreland.

DR. MORELAND: Range.

CHAIRMAN PETRI: Ms. Malone.

MS. MALONE: I tend to go to range, but I'd really like a clarification of what he means by bar.

CHAIRMAN PETRI: Well, Dr. Simon suggested -- and, obviously, this doesn't have to be the definitive answer -- that 30 minutes be the bar, and if the onset to meaningful pain relief was within 30 minutes, it met that.

MS. MALONE: Okay.

CHAIRMAN PETRI: We're not going to vote on whether it should be 30 minutes, 40 minutes, 50 minutes. I think that's going to depend on the disease and the pain model, but this idea that a bar -- is that sufficient? Is that your choice?

MS. MALONE: I think I tend towards the range, but again whatever it is has to be explicitly said so that it's understood. So I think you could go

with either one as long as that's explicitly stated.

CHAIRMAN PETRI: Dr. Liang.

DR. LIANG: I concur with her.

CHAIRMAN PETRI: Dr. Tilley.

DR. TILLEY: Obviously, range.

CHAIRMAN PETRI: Dr. Simon. If you don't vote for your bar, we're into a little trouble.

DR. SIMON: You're going to love this one. I would like my bar expressed as a range.

CHAIRMAN PETRI: Dr. Fernandez-Madrid.

DR. FERNANDEZ-MADRID: Range.

CHAIRMAN PETRI: Dr. McGrath.

DR. McGRATH: Range.

CHAIRMAN PETRI: Dr. Yocum.

DR. YOCUM: I will say that I'm against regulating fast in the OTC market, but if we're going to do this, a range.

CHAIRMAN PETRI: I vote for a range. Dr. Pucino.

DR. PUCINO: I vote for a range, because I think a bar -- it will be a constant moving target.

CHAIRMAN PETRI: Dr. Koda-Kimble.

DR. KODA-KIMBLE: Range.

CHAIRMAN PETRI: Dr. Callahan.

DR. CALLAHAN: Range.

CHAIRMAN PETRI: Dr. Tong.

DR. TONG: Range.

CHAIRMAN PETRI: Dr. McKinley-Grant.

DR. McKINLEY-GRANT: Range, because I agree. A bar is a range. It's from zero to 30 minutes. But range.

CHAIRMAN PETRI: Dr. Brandt.

DR. BRANDT: Range.

CHAIRMAN PETRI: Now this may have been one of the most difficult votes we ever did, but I'm now going to move on to question 3.

What are some recommended study designs to establish fast analgesic claims?

So we're getting rid of that word fast.

DR. BLEWITT: Madam Chairman?

CHAIRMAN PETRI: Yes, Dr. Blewitt?

DR. BLEWITT: I just need to ask this question again. It's a range for what?

CHAIRMAN PETRI: For the onset of meaningful pain relief.

DR. BLEWITT: Of what kind of pain?

CHAIRMAN PETRI: We said that this would have to be defined for each pain model, that this is not something that will generalize to every pain model.

DR. BLEWITT: Then where that data -- where those data don't exist, they now have to be generated for --

CHAIRMAN PETRI: Of course. I think this committee has stated unanimously that we prefer data. Dr. Tilley.

DR. TILLEY: Barbara Tilley. We're not asking for a range for every pain model. We're just saying some pain model range, you know, whatever that pain model is that you happen to use to get your claim, not that you have to have a pain model for every disease.

CHAIRMAN PETRI: No, of course not, but if someone wants to get into this can of worms, then they better do it with some data.

DR. BLEWITT: Well, I'm only suggesting that -- and Dr. Soller raised this and Dr. Weintraub mentioned it -- if you go to each pain state, since currently marketed analgesics are actually marketed for a number of pain indications, then you're going to actually have to provide data on each of those pain states, and that -- I'm just not sure how much the consumer will be interested in reading all of that information.

I also feel that there is a major space

issue that will come up with regard to OTC labels. You know, there's just only so much meaningful information that can go onto a label, and a lot of that should be addressed more to safety, I think, than to time -- you know, time to meaningful pain.

CHAIRMAN PETRI: Well, I don't think that we can necessarily worry about what's going to be squeezed on the label today. I think we need to ask, is this something that the consumer, the patient, the physician would like to know.

Let's have a few questions from the audience, first the microphone, then Dr. Ehrlich.

MEMBER OF THE AUDIENCE: Dr. Nicole Fidagio. My question is addressed to the issue of the design and the kinds of things you're going to measure in a trial.

As I understand it, very few studies, relatively speaking, in pain have used this endpoint of using stopwatch, but there's a great number of studies which have used other measures such as pain intensity difference or relief of pain scales.

So that means if you -- As I understand the discussion, if you propose that meaningful is the endpoint, then lots of new studies have to be done, and all the old studies have to be just thrown away.

We cannot rely upon historical data to make any decisions.

So I would ask the committee to consider that there should be some way of matching the two up. If you're going to have meaningful as your criterion, that somewhere along the way you want to try and match it to some scales which are somewhat more continuous than these yes/no scales and are, therefore, much more informative for trying to make decisions about pain. First point.

The second point relates to, if you do that, it also allows you to get around the problem of manipulating designs to choose weak pains against strong pains. That is, you use scales which allow intensity of pain to be part of the claim that is being made and not simply ignoring the fact that pain has different intensities, and only dealing in the time domain which is all the discussion has been involved with today.

Meaningful, without reference to the intensity of pain, I think, opens more questions than a scale that does recognize intensity of pain.

CHAIRMAN PETRI: Dr. Ehrlich. Then Dr. Laska.

DR. EHRLICH: Thank you. I hear a problem

around the table that I think Leigh Callahan clearly tried to address, which is how is all this information communicated.

It's one thing that the information be gathered and submitted to the FDA for approval, for monograph or whatever. It's another thing, the communication. The label can hold only so much. It isn't going to communicate everything.

Advertising does a lot of things. If the information is on hand, advertising sometimes is used to communicate certain information that may not even be on the label, but it is appropriate, and there are articles and so forth.

The public learns about drugs that they buy OTC from a number of different sources, and I don't think that the label is the only way they learn about it. So I think that's where some of this confusion comes, because it's not all going to be compressed on the label.

Of course, the agency gets the information from the studies, and then what's done with that, that's another story.

CHAIRMAN PETRI: But I don't think that we can solve that today. So I've asked us to have sort of simpler goals for our discussion.

Now everyone has been very concerned about study design, and that's what question 3 is about. So again what are some recommended study designs to establish fast analgesic claims? We're getting away from that fast. So let's substitute, what are some recommended study designs to establish the range of the time to onset of meaningful pain relief?

Let me just ask our experts. We all sort of understand that stopwatch study design. It seems something that we could easily explain to a patient or a consumer. Will that stopwatch design generalize to other pain models besides dental pain? Could we generalize it to osteoarthritis? Dr. Laska.

DR. LASKA: To answer that as well as Dr. Hoagland, it's important to understand, for those of you who haven't been involved in this, we have not abandoned the traditional analgesic clinical trial methodology. The stopwatch is an added parameter that's both clinically collected and statistically analyzed, and it puts a lie to the notion that there's one number that can characterize what an analgesic is all about.

One must describe the properties of their time and effect curve. The clinical trials that have been done have been broader than simply dental pain.

Dental pain is a nice, clean place to do the work, using the word clean that someone else used before, but it's certainly been done in headaches by Dr. Sunshine and others, and there's no reason to believe that it would be limited to this circumstance.

The complexities have also been examined in outpatient studies with patients who have been asked to go home with migraine and take -- use a stopwatch to see, when you don't know when the event, the painful event, will take place.

So it has been used in a wide variety of circumstances, and I think the design or the use of this as an added instrument is generalizable. In other circumstances it's possible to do the same kind of questioning again, and address the issue without the use of a stopwatch, for example, in chronic use studies.

Going back to my depression example, there's no stopwatch in that. There are interviews on a periodic basis, and they are -- The time is measured in days rather than minutes. I think these --

CHAIRMAN PETRI: But you would still get to the two key points that the committee has brought out this morning. We want to know the percent of responders. We'd like to know the time to meaningful

pain relief. Those two things are generalizable. The study designs currently available will be able to capture those.

DR. LASKA: Exactly. That's been proven by people who have done these kind of studies.

CHAIRMAN PETRI: Let me -- Dr. Brandt first.

DR. BRANDT: We, in fact, have some experience with that in OA of the hand and OA of the knee, and it was very problematic. In those instances we did baseline pain and administered a fast acting analgesic, and then we tried to boost the pain by repeated stressing of the hand joints or walking the patient around the football field to try to increase pain.

The reproducibility was impossible. It was just not satisfactory.

CHAIRMAN PETRI: Okay.

DR. LIANG: With a stopwatch, Ken? With a stopwatch technique?

DR. BRANDT: Administering an analgesic both at baseline pain and after we had increased the pain as a result of standardized physical activity, and using a stopwatch to look at the pain relief. It just simply was not reproducible in either setting.

CHAIRMAN PETRI: So we've got a problem with at least one pain model, osteoarthritis. So it sounds like the methodology still needs to be developed.

Let me ask Doctors Weintraub, Hyde and Katz, what other things did they want to bring out with this question.

DR. WEINTRAUB: I believe that the discussion this morning has been very useful, and we've brought every -- pretty much everything.

Now the designs we're interested in -- the possibility of the designs that we would like to hear discussed -- I think this could easily be the last thing that has to be discussed, if you want to do that.

CHAIRMAN PETRI: Very subtle again.

DR. WEINTRAUB: Well, I won't say how one learns to do that. Hitting you on the head with a hammer would accomplish the same thing.

Okay. We need to know a little bit about the size of the studies, about whether or not it can be integrated into the previous studies. Of course, Dr. Laska said yes already, and I think that's pretty well taken care of, but the size of the studies and whether or not there should be a special type of

study.

Now John, did you have anything that you were thinking of?

CHAIRMAN PETRI: So I think one thing the committee has brought out is that we think these studies have to be done within each of these different pain models, unless someone can tell us that the time to meaningful pain relief is going to be similar in different pain models. I think that's what's upset most of us, is the absence of data.

DR. WEINTRAUB: Well, one thing we learned today was -- Actually, Dr. Liang who threw it out as a point to consider -- was that it was something I hadn't thought of anyway of standardizing the pain model and saying, look, if you take dental pain or if you do take this pain model, here are the data; and that would be sufficient perhaps.

So, you know, is that a reasonable approximation of what you said?

DR. LIANG: As a minimum, and that if you had it for OA or whatever, you could add it on.

CHAIRMAN PETRI: Ms. Malone.

MS. MALONE: It would just seem to me that it's extremely sensible that, if you're making a claim that this is analgesic for a particular ailment, that

you would have the data. You know, how else could you make the claim?

CHAIRMAN PETRI: Dr. Liang will respond.

DR. LIANG: My understanding of analgesic is that it's not -- You know, it's a pain -- something that gives pain relief, period.

MS. MALONE: Okay. So it's like generic.

DR. LIANG: In fact, we use it medically without having to make "a diagnosis," necessarily. It's not one of these things where we would use it, thinking that we knew the pathogenesis or anything else. It's a symptomatic relief, though.

MS. MALONE: Okay. So you're using pain in a generic term?

DR. LIANG: That's my cut on analgesics.

MS. MALONE: Okay. But if on a specific over-the-counter -- you know, on the label where they put "for use for" -- if you're making --

CHAIRMAN PETRI: General pain, headache, dysmenorrhea.

MS. MALONE: Yeah, but if you're making the specific claim, you have to have data to back that up if you're mentioning a particular disease or ailment, in my book.

DR. LIANG: I would be smart and not do

it. I would just tell people this is a general pain relief medication.

CHAIRMAN PETRI: Let me have Dr. Weintraub remind the committee again about the label for analgesics. Dr. Hyde.

DR. HYDE: Yes. For things that are under the tentative monograph, you know, they're specified as being recognized as analgesic and are given a list of indications which they're allowed to use.

For products that were NDA that then went over the counter, typically they were studied in a couple of pain models, usually being dental and post-operative, but from that they're allowed to generalize to, you know, things other than specific things it states, such as OA/RA and dysmenorrhea. Those need to be investigated separately, but otherwise, you know, it's recognized as an analgesic and most of the things that hurt you are where it should work.

So, you know, I guess traumatic conditions might not necessarily be studied. You know, over-exertion, muscle pains might not necessarily be studied, with the general consensus being that things that are analgesic and standard models, you know, in our experience it's quite reasonable to extrapolate, and we do.

CHAIRMAN PETRI: Comment from the audience first. Then Dr. Max.

MEMBER OF THE AUDIENCE: Al Sunshine. Dr. Hyde, I think you raised a very important point about what model. For OTC analgesics, I think the suggested models are dental pain, the pain of sore throat which I think, by the way, is best treated probably with penicillin rather than analgesics to prevent rheumatic fever, but we'll leave that aside, muscle aches and pains. Then you have headache and dysmenorrhea.

As Dr. McGrath pointed out, in the 26 years that the monograph is under consideration things have changed, and surgery has moved as an outpatient -- I mean patients go home very quickly, and many surgical procedures are done in ambulatory care facilities. So the decision of what analgesic to take is left -- after an operative procedure is left in the outpatient environment.

I would suggest that the committee and the FDA consider adding post-operative pain as a pain indication.

The other thing is the patient selection you have is a relatively young one. Dental extraction is done average age 25. Sore throat is a disease of younger people as a rule. Dysmenorrhea is in the

childbearing age range, and older patients who are taking this medication are really left out.

I would also -- Since there are a lot of rheumatologists in the room -- ask if OA is a consideration as a pain model. They have more experience than I in that, but I think that is an area that affects a lot of people, and as we know, the aging population may respond differently than the younger population.

CHAIRMAN PETRI: Dr. Sunshine, I think Dr. Brandt brought up that point about OA not having the methodology at this point. Dr. Brandt could you just respond again?

DR. BRANDT: With regard to rapid acting?

CHAIRMAN PETRI: In other words, defining the time to meaningful pain relief for OA. You don't think the methodology is available at this time?

DR. BRANDT: Well, with our limited experience, that was correct, but I'm not sure that rapid onset of action is important in the chronic of osteoarthritis either.

CHAIRMAN PETRI: Dr. Max.

DR. MAX: If you decided to select a single model to get a noncomparative time of onset and, say, you pick dental pain, which is a reasonable

choice, I think you need to further specify a -- There are standard trauma scales for the number of teeth extracted, a certain range of trauma scale to equalize it. Otherwise, I'll be advising industry tomorrow to take one upper tooth out.

CHAIRMAN PETRI: We all agree that the methodology must be clean. Now I think it would be unfair to end without giving people a chance on question 4.

So what types of comparative product claims could be allowed? Many people -- I told you to table the faster. So now I'm going to allow people just to say whatever they would like to say. So all those of you who have been quiet -- Dr. Fernandez-Madrid.

DR. FERNANDEZ-MADRID: None.

CHAIRMAN PETRI: None. Anyone else have a thought here? Remember, if it is possible with a methodology to define that range of onset as meaningful pain relief, statistically you could allow a comparative claim if the ranges do not overlap. So let me ask Dr. Tilley if she could respond. Statistically, this could be done?

DR. TILLEY: There are methods to compare these distributions, but the issue would be the model,

which is, you know, if you're making this comparative claim, are you testing -- you know, what model are you testing it in, and who are these patients?

CHAIRMAN PETRI: I think the committee --

DR. TILLEY: It's just the same issues that we face anytime we make a comparison of any drug.

CHAIRMAN PETRI: So I think the committee is concerned that the methodology is not there, but if it were, comparative claims could be done. Dr. Simon.

DR. SIMON: With the caveat that statistics may not be clinically important. So, yes, we could perhaps distinguish between one and another product, but a consumer would never know the difference.

I'm very concerned about legitimizing the effort to do that. On the other hand, I'm also very concerned about the development of technology that can actually allow us to understand the effectiveness of these agents and the efficacy of these agents.

CHAIRMAN PETRI: Dr. Max, then Dr. Tong.

DR. MAX: I think if the FDA wanted to get into comparative claims, the only thing that makes sense to me is to select one standard preparation that might be -- that's likely to be available for the next, say, ten years to create a level playing field

and say this drug is ten minutes faster than standard ibuprofen made by such and such a place.

If one is just concerned with a claim that Advil wants to claim that they're faster than Tylenol or Tylenol is faster than Advil, I'd be happy to leave that to the courts. If they can do a trial and show that they're faster than the other and put an ad in the paper or TV and have it stand up, I don't see that we need to get into that.

CHAIRMAN PETRI: Dr. Tong.

DR. TONG: Related to the question about claims and what Dr. Simon was saying, it's been really instructive today to discuss this issue of what's fast and faster, but I'm reminded of my mother-in-law who asks me more often what does powerful and more specific mean, rather than what's faster. She can understand that one, but as a pharmacist she's asking me, tell me about more specific and more powerful, and I hope this group may not want to address that.

CHAIRMAN PETRI: Your point is well taken, and let's refer back to our previous discussion. We all wanted to know the percent of responders, and we wanted to know duration. There are so many things that are equally as important.

If we get into this, then I think those

have to be emphasized just as much. Dr. Hyde has a comment.

DR. HYDE: In response to that, I'd like to say -- I mean, the things that don't really mean anything we're not too concerned about. I guess it's the things that consumers might attach significance to that would be our concern. Are they really getting information they think they are getting?

CHAIRMAN PETRI: I'm going to ask Dr. Weintraub if he'd like to make some closing remarks for this morning's session.

DR. WEINTRAUB: I sort of wish sometimes, Dr. Petri, you didn't know my name.

This has really been very instructive for us. It shows you the complexity of the issues we have to deal with. On the other hand, I do remind you that this is early in the process, and it's only about analgesics; but this is not going to go away, and we can't disregard it, and we're going to have to take some kind of action.

You know, I would like, too, to say we're not going to handle this. We're not going to pay any attention to it, but I don't think so. I think we will have to pay attention to it, and we will have to handle it.

I do want to finish up by saying that the discussion this morning has really been very helpful to us. I think John and Linda would agree with me that many important points were brought out, very reminiscent of some of our sessions that we had internally, but it's good to see that we're just -- that the problems we face are generalizable.

It made us feel good that you had trouble with the same things we had trouble with and wished that certain things would go away and wished that certain things would -- you could handle certain things in a clean manner, but anyway it has been very helpful.

CHAIRMAN PETRI: Now we will adjourn, and we will reconvene at 1:30 to take on acute versus chronic pain.

(Whereupon, the foregoing matter went off the record at 12:15 p.m.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:31 p.m.)

CHAIRMAN PETRI: This afternoon we're going to be talking about the pain claim structure for chronic and acute pain, and I'd like to turn it over to Dr. John Hyde who is going to give us an introduction and overview of this afternoon's topics. Dr. Hyde.

DR. HYDE: Okay. Thank you, Michelle. This has some similarities to this morning's --

CHAIRMAN PETRI: Not too much, I hope.

DR. HYDE: Some differences. This is also sort of the opening cell, though, in the initiative to develop some guidance concerning the pain claim. So this is the first step, and it's not anticipated that we will conclude everything today.

Some differences as far as the motivation and sort of a complement to this morning's session -- It more comes from some concerns we've had inside the agency, but with some component of inquiries we've had from outside as well.

It might be useful just to recap the current basic framework for analgesics. The usual application that would be aimed at an analgesic indication, and there are some guidelines in the back

of the materials you've been handed out.

It usually would include -- What we ask for is replicated studies and two pain models, and typically what we'll get is actually several dental pain studies, often several post-operative/post-surgical, orthopedic being a common example, post-operative pain models.

Dysmenorrhea is frequently used, although that is recognized as a separate indication and would be so indicated in the labeling. OA and RA, while they are painful conditions, have specific guidelines that this committee has looked at and worked on, and are recognized as specific indications.

So that the typical application will include probably half a dozen or more actual analgesic studies, and in conjunction with that there will be -- I'm sorry. I should go back and say usually the dental model are usually single dose studies. Post-operative usually involve multiple dose for a number of days.

Then there will be a safety database frequently in OA patients, but not for the OA indication necessarily, and it may be a mixture of other chronic pain conditions to get a safety database for the drug; and depending on the type of drug, it

may range from like one to three months typically for narcotics and usually up to six months if it's an NSAID.

The outcome from that will be labeling, and that includes an indication for pain, not otherwise qualified. Now -- and that's part of what we want to discuss today. You know, do we want to change that and modify that?

We have sort of inconsistently sometimes qualified the pain, mild, moderate, severe, usually with sort of the coding that severe means some situation where an opioid would generally be used. So most of the NSAIDs wouldn't go up to that. They would either not quantify the pain or else would not include severe pain in that.

Recently, we've also had some limitations to acute pain, and specifically we've had acute products. Bromfenac and also toradol have restrictions in the duration of the uses, primarily based on safety concerns with the drug, but the committee may want to discuss the efficacy aspects of that, too.

So anyway, the reason this is coming up for the committee is there's some aspects of this we haven't been completely comfortable with, and we want

some further discussion of.

One case in point would be neuropathic pain, and we sort of generally recognize that the things we approve for pain don't necessarily work for neuropathic pain, and what should we do about this. Is the situation adequate? Should we quantify it? Should we do something special with neuropathic pain?

Another issue that's on the agenda is the acute versus chronic. Except for the recent cases, we haven't done anything -- we haven't specified it in any particular way, and one issue for discussion is do we want to recognize these as separate indications and label them separately, study them separately? How do we want to deal with that?

One of the reasons to consider this is to provide possibly some incentive for studying specifically chronic pain conditions. Under the current situation, as long as you get a pain claim, you could still do the dental studies, do a few post-operative studies, and then go and sell yourself as the low back pain drug. There's currently nothing really to stop that approach.

Another issue has to do with the multiplicity. If we decide that we really want to subdivide pain claims, there's a question of how far

do we want to go, you know, divide it out into subtypes; and there's a potentially unlimited subdivision you might want to do. How are we going to deal with the -- Can we make some rational groupings? Can we set up criteria for studying broad groups?

Finally, this sort of feeds into some other initiatives within the FDA. The FDA is currently working on a general efficacy document to deal with some of the issues of multiple indications, in particular, trying to move away to some degree from the formal requirement of replication of studies in each particular indication, and looking if there are related indications that could be used to bridge or work together to get a specific indication.

So some of the discussion today, I think, will help feed into that and shape that discussion.

Now the purpose today is not really to come to final conclusions on these, but really just to put these questions before you and before the public and to begin the discussion.

Now if you are troubled by the lack of data this morning, it's even worse this afternoon, because there really isn't much in your jacket; and because of the way the indications are set up, we really haven't seen them studied too much differently

from what we currently do.

So it's going to be partly a philosophical discussion at this point, but I hope we can get something useful out of that, too. Also, if you want, there are some questions here, but if you have other questions that you think we need to consider and put before the public, please feel free to add that, too.

Another thing: If you have suggestions on what other next steps we might take to help address these issues, that would be fine as well. So let the discussion begin.

CHAIRMAN PETRI: Thank you. I'll ask us to focus the discussion on the questions, and again I will invite audience participation, encourage it.

The first question is: How should pain claims be categorized? Let's first discuss the issue that Dr. Hyde brought up, acute versus chronic pain.

Maybe we could start off with are there different types of pain or are acute and chronic pain similar enough that we can group it? Let's specifically think about this idea: Can you have an indication for pain if your only studies have been in acute pain models?

Let me start with Dr. Laska.

DR. LASKA: This is a difficult one to

comment on in the absence of specific pain studies which show otherwise, but in the studies of chronic pain -- we heard one this morning from Dr. Brandt -- where failures occur, they tend to occur more often in the chronic pain situations where you can't tell drugs apart that you thought you were going to be able to distinguish.

That happens for a variety of reasons, some of which are speculative and some of which are absolutely -- don't rise to the level of speculation -- sheer guesswork.

So I don't believe that this is an easy one to answer from the point of view of philosophy. I believe it's data driven again, like much of the comments this morning. But in the studies I have seen of chronic pain where the models have been consistent with acute pain, the parameter values tend to look the same. Things get to have an effect difference of around the same size, but the level of failures goes way up when you compare drugs of chronic pain levels.

You can't tell apart things that you thought you were going to be able to distinguish.

CHAIRMAN PETRI: Can you comment on whether it should be possible to get an indication for pain based only on studies in acute pain models?

DR. LASKA: No, I don't think I can comment on that.

CHAIRMAN PETRI: Dr. Max.

DR. MAX: First, to start with, what there's data for. The only drugs for which you can compare acute pain and chronic pain studies are the NSAIDs, acetaminophen and the opioids. There, there are a number of conditions.

These drugs all work for many acute pain conditions, and they work for cancer pain, various arthritides, various chronic musculoskeletal disorders. So there is a reasonable correlation there, but once you leave that, there are almost no published trials, and it's only now that there are a group of new drugs coming out, and there's a raft of new drugs.

I mean, every major company has some drugs. Then you get into a fundamental scientific question, which is: Is pain one thing, all kinds of pain having similar mechanisms, or is it many things?

The truth is no one knows the answer yet in the absence of a body of clinical trials. I can -- The academics tend to be splitters, and I work in a group, more than half of which are basic scientists. So academics tend to be splitters, and there's a lot

of information.

Certainly, neuropathic pain is different in mechanisms than other kinds of pain, because there's a distinct anatomy. Once you injure a nerve, you have sprouting of the neuroma at the injury site which has ectopic discharges. You have discharge from the dorsal root ganglia, and you have changes in the central wiring.

There are specific anatomical differences, and there are some differences in drug responses in a small number of academic trials, but if you talk about other pain conditions, there are some reasons to believe that -- the basic scientists would have you believe visceral pain might be a little bit different, some slight differences in the anatomy in the pharmacology coming out, but there's no body -- There are essentially no clinical trials aside from dysmenorrhea published in chronic visceral pain.

I just asked -- Before this meeting I asked Jerry Gephardt, the leading basic scientist in visceral pain about this meeting. He said, we can't generalize my findings from the gut to the bladder. I mean even to generalize from one visceral pain to another is not something you could do.

So -- and there just aren't studies

comparing acute and chronic pain with the other compounds to allow that validation. If you take even neuropathic pain -- that's been a main focus of my research for 15 years -- there's very nice correlation with a few drugs, with tricyclic antidepressants work and have similar efficacies and similar individual drugs correlate well between diabetic neuropathy and post-herpetic neuralgia. However, we've just done several studies with NMDA blockers with dextromethorphan and found a differential response. DHN didn't respond.

With NIAV we've completed a couple of large trials in AIDS related neuropathy where tricyclics didn't work at all. The biggest group of all with neuropathic pain are those -- probably ten times as many people have neuropathic pain from spinal root compression, cervical or lumbar, than with diabetic neuropathy; but there are almost no clinical trials whatsoever, and I would hate to give someone -- give a company an indication for general neuropathic pain. They ought to be studying neuropathic spinal pain if they want a general indication.

So the answer is there really is -- There's just not the data, and when I sat around at meetings with drug companies with some of the leading

basic scientists, and the company says here we have a fantastic new drug. It's a lizard venom from South Africa, and it works in this rat model of neuropathic pain, visceral pain, arthritis pain, etcetera. What conditions should we study it for in chronic pain?

You know, the most brilliant basic scientists in the world say, how the hell should we know? There is no data. We just -- We really don't know.

So I think in general we're going to need another ten years of clinical trails to see what the kinds of general patterns are. Our pack includes a very nice piece of work by the OTC group for a few years ago, but they had about 10,000 published clinical trials, and they could see where you can generalize and where you can't.

There just isn't any clinical work, and the basic data is very -- at the beginning.

CHAIRMAN PETRI: But to summarize, you don't think that we can split acute and chronic pain, but you think there's enough information to split off neuropathic pain?

DR. MAX: Well, each one is a discussion. I think one needs to be very small and data driven in what you approve. I think it's a danger to give

approval for a drug for a large category like -- I don't like chronic pain as an indication for a drug, because it would foreclose clinical research on the many kinds of chronic pain.

If we say you study chronic bladder pain, and you get an indication for chronic bladder pain. That will leave an incentive for the next year for someone to study chronic gut pain or chronic arthritis pain.

We have no basis for generalizing at this point.

CHAIRMAN PETRI: In rheumatology, we have an example of fibromyalgia, a chronic pain condition where antidepressants help more than NSAIDs would. An example, acute versus chronic pain being approached in a different way.

let me ask Dr. Brandt to summarize his OA experience as a good example of a chronic pain.

DR. BRANDT: Well, I'm not entirely sure what you mean by summarize my experience, but I guess we should say that the issue that we addressed a few years ago was whether there was superiority to an anti-inflammatory relative to a simple analgesic acetaminophen in palliation of palliation of knee pain in patients with moderately severe osteoarthritis.

We looked at an anti-inflammatory dose of ibuprofen, an analgesic dose of ibuprofen, and acetaminophen in a dose of four grams a day for a four-week trial. The results of the study indicated no clear superiority of the anti-inflammatory versus the -- either of the analgesic regimens.

I think the other -- I think that was a four week study. We have no data there with --

CHAIRMAN PETRI: Was there a placebo?

DR. BRANDT: No, there wasn't a placebo included there. All of those have been tested previously against placebo, and been shown to be superior to placebo.

We could not -- Even in those patients who had inflammation histologically on synovial biopsies in one group or clinically on the basis of physical examination, we couldn't predict the superiority of the anti-inflammatory regimen over the analgesic regimens.

I think the -- Our interpretation is that the origins of pain in osteoarthritic joints are multiple, and synovial inflammation, even when it's present, is not necessarily the origin of the pain. It may originate from bone. It may originate from muscle spasm, from capsule, etcetera, etcetera.

I think beyond that, the other point I would make is that -- and I think this has relevance to clinical trials and to patients in those trials -- that there have been -- It's been shown that there are a number of nonpharmacologic measures, some of which are very routine in clinical practice by primary care docs and specialists, that are as effective as either analgesic or anti-inflammatory medications in symptomatic treatment of OA.

The results of the comparative clinical trial I just mentioned, in fact, I think, should have been predictable, because while there had been up until that point no head to head comparison of an anti-inflammatory versus an analgesic in OA, there were several studies comparing one anti-inflammatory -- one NSAID with another with another, and in many instances the comparator was Ibuprofen in a dose of 1200 milligrams, which was, in fact, one of the arms of our study, and 1200 of Ibuprofen which minimal -- I think people would agree -- minimal anti-inflammatory effect was as effective in those other trials as anti-inflammatory doses of other NSAIDs, including phenylbutazone in a dose of 400 milligrams a day.

So I think in this particular context the

issue is -- I think our perspective would be that OA has an element of inflammation very often, true, but for symptomatic relief it may not be necessary to treat that inflammation. Whether that inflammation in the long run does harm in terms of driving the progression of joint damage is a separate issue which those studies can't address, and I think it's still very much open to question, but dealing with palliation of joint pain and symptoms, there are those data and others that would support that.

Clearly, individual patients do better in some instances with an anti-inflammatory than with an analgesic, but I don't know how to predict which patients those will be.

CHAIRMAN PETRI: Could you also just update everybody on the committee about things such as capsaicin, an example of something we would use for osteoarthritis which we would never use for acute pain?

DR. BRANDT: Yes. Some people wouldn't use it for osteoarthritis. There are three or four studies, placebo controlled studies, which have shown efficacy of topical capsaicin application in comparison with the placebo; and the placebo was a little tough, since there's burning that develops with

local application in half the patients at least who receive capsaicin, but studies of hand OA, studies of knee OA have pretty consistently shown some efficacy.

In most of those studies, the capsaicin has been added to a base of NSAID or analgesic therapy, but there was a study by Altman in which it was tested as monotherapy and was also effective.

CHAIRMAN PETRI: So I think we're starting to get examples of different approaches to acute and chronic pain. Dr. McGrath.

DR. McGRATH: Patricia McGrath. I just wanted to say that I think that at present we don't have the information to support the term chronic pain as meaningful. I would say it's meaningless in terms of a category for pain claims.

Dr. Max mentioned the issue with respect to neuropathic pain, but I think that you can make that same issue with respect to a lot of different types of pain that would fall under the rubric of chronic pain, and that perhaps in any kind of labeling pain claims, we need to really look at features that would be -- features of a pain complaint that would respond to that particular analgesic category in the same way that initially we talked about pain, minor to moderate pain associated with X, Y and Z for some

labeling.

There could be features that are associated with inflammatory pain that go along with some chronic pain conditions, but I think the name by itself really does not connotate a specific enough meaning for this.

CHAIRMAN PETRI: Can you give us an example of how you would start to do that? What are the features of what we now call chronic pain that would allow us to better categorize it?

DR. McGRATH: Well, I think some have to relate to mechanisms. So we're talking -- I guess when I talk about mechanisms in differential diagnosis, I think more of prescription type drugs rather than OTC, and that may not be relevant for this conversation.

If you are looking at, for example, aspirin, acetaminophen, nonsteroidals in general, there are features of inflammatory pain. There are features on cancer pain, for example, where you would be using traditional opioids as well as those categories.

So there may be something to do with pain typically associated with -- and then name a condition. Does that help?

CHAIRMAN PETRI: Well, as a pain specialist, if someone comes to you with what I would feel comfortable calling chronic pain, how do you dissect it, and does that dissection then determine what medications those patients will take? Dr. Max?

DR. MAX: The standard method that the pain specialists, along with pain scientists, are trying to teach the generalists in writing textbooks is to sort out the pain by tissue.

So if you see someone who says I have pain deep in my back and there's no clear understanding of what it's from, you try to say is this coming from nerve? Is it myofascial? Is it coming from muscles? Is it coming from bone to joints? Is it coming from viscera?

Given that classification, then you look at the list of drugs that you know work for that. Neuropathic pain -- now there are clinical trials to show six or eight different classes of drugs work. So you'll try those, if you think it's nerve.

If it's myofascial -- I mean, all we've got are tricyclics and Flexeril, you know, pretty much. Visceral pain, there's very little. So we try to sort it by tissue. We tried to sort out the presence of inflammation or not.

Another very common distinction now is there's the -- In many kinds of pain, there is central sensitization, which is a central counterpart of peripheral inflammation where the neurons -- the gain is turned up, and there are some drugs being introduced that may relieve that.

It's very difficult in an individual patient if you don't have two days of quantitative sensoring testing in a lab to establish that, but that's about where we're at right now, and theory goes ahead of firm knowledge.

CHAIRMAN PETRI: Dr. McGrath?

DR. McGRATH: I think that you've explained it very well, and I would almost look back and say, from a layperson's viewpoint, I might view acute pain and some of the claims that we us for some of the OTC analgesics as really being a very clear model in terms of peripheral activation of no susceptive afferents, a clean system, as clean as it can be in general. Whereas, in chronic pain you have a variety of etiologies, usually the multiple etiologies as you've just mentioned.

You can have -- and you have to really almost look at the mechanism in deciding what category is going to be best for which patient. I think with

headaches, for example, there's chronic daily headaches, that a patient could come in with a lot of the symptomatology of somebody who had recurrent tension headaches, and yet the diagnosis and the pain complaints -- some people might consider those both chronic conditions if the patient had had tension headaches frequently, but the actual drug you would give would be very different, depending on -- Probably you give tricyclics to one person and analgesics to another.

So I think it really has to do with characterizing the systems involved in chronic pain in a different way than acute pain.

CHAIRMAN PETRI: Now the message I'm getting so far is that you do think that there is probably both a basic science and a clinical reason to differentiate acute and chronic pain.

There's a comment from the audience.

MEMBER OF THE AUDIENCE: I'd like to comment and see if I can frame this debate. Certainly, I think Mitchell Max and Patricia McGrath have -- My name is Najib Baboul. I'm with Cyrex.

Certainly, Patricia and Mitch have framed the debate appropriately in terms of some of the issues that we need to look at. I mean, I think if we

thought we had challenges in the morning in exploring the issue of onset with acute pain, we've got out work cut out -- the committee has got its work cut out this afternoon.

If we look at the current approach to labeling for pain, certainly one can make a reasonable case that that has served us well, in that you get an approval for pain -- a general pain management approval, and then the CLIN form section provides the clinician with the guidance in terms of its actual utilization in practice.

Certainly, on could make the case for some degree of additional specificity to the claim indication, and it's not unreasonable to have framed the debate in the context of looking at specificity with respect to intensity and chronicity; and to the extent that we tend to think of acute pain, chronic pain, neuropathic pain perhaps as a subset, and cancer pain, that would on the surface appear reasonable, but I would caution the committee in terms of generalizing chronic pain as a pharmacologically homogenously responsive group.

Let me just illustrate the point. I would argue that it is probably reasonable to expect that, if you look at a clean model of nociceptive chronic

pain, that an NSAID or a drug that reproducibly is effective as an analgesic in acute pain is likely to demonstrate efficacy in that chronic pain model. However, I would also argue that, if we were to look at chronic pain versus acute pain, many of these drugs that will be effective in clean models of nociceptive chronic pain would not be effective in a large number of other chronic pain models.

Myofascial pain is one example where there is virtually no data. Fibromyalgia is another pain state. However, if you were to study it in OA, you would likely find a responsiveness.

So I think that this arbitrary categorization in acute and chronic pain probably is not likely to serve us very well in terms of predicting the pharmacologic response to drugs.

CHAIRMAN PETRI: But let me challenge you. What is the next step?

MEMBER OF THE AUDIENCE: Well, I would say again that one can make a reasonable case, and I think one of the things that it would be worthwhile knowing is what are the problems with the current approach to labeling where we obtain a general management of pain indication and, to the extent that one wishes to promote a drug for a specific pain state -- for

instance, if one were to look at chronic low back pain, then in fact you would have to show evidence, you know, to the satisfaction of the agency with respect to, you know, advertising for that indication.

So what I am saying is that myofascial pain has generally demonstrated not to be terribly responsive to pharmacologic agents. Fibromyalgia has demonstrated not to be terribly responsive and, you know, Dr. Max has just indicated to us that there are agents which may demonstrate efficacy in post-herpetic neuralgia but perhaps not demonstrated efficacy in diabetic neuropathy or some other neuropathic pain states.

So I think we need -- Clearly, we need more studies in specific pain subtypes, but to categorize the data into acute, chronic, cancer and neuropathic -- Neuropathic, I think, as a group probably is worthwhile looking at separately, but chronic pain runs the risk of allowing for utilization in pain states where no data exists.

CHAIRMAN PETRI: Dr. Max. Thank you. Dr. Max.

DR. MAX: My suggestion is based on the situation that right now NIH and academic -- the academic community supports pain research -- chronic

pain research only in a few areas. There's a smattering of neuropathic pain research, and virtually no clinical research in any kind of visceral pain, GI, GU, gynecological, etcetera.

You know, there is, obviously, arthritis research. I think -- and industry is very conservative. You know, for their claims they've been using time tested models, and they are very loathe to develop a brand new model if they don't have to.

So industry gets a new analgesic. They'll do them in dental model and other surgical models, and these days they may have -- if it works in rat neuropathic pain models, they may try it in diabetic neuropathy, but it leaves most of the pain conditions from which we suffer unstudied.

Physicians, we have no information on how to study it. So I would propose using a claim structure as an incentive to get industry, particularly small companies, to study to get a bit of a niche with good research.

I'm afraid, if you have a chronic pain indication, then the big rich company might get a general indication and overwhelm the market with their funds, with resources, with advertising; whereas, if you said you have to just come in with a well

demarcated group like, say, bladder pain or diabetic neuropathy or -- then a small company could come in and do maybe one trial with dose response in that condition, and there would be much greater incentive to get more facts.

It might be that ten years from now we would have enough data to create a more general structure, but I'm arguing for this incentive to get more data.

CHAIRMAN PETRI: Okay. Dr. Brandt.

DR. BRANDT: May I ask a question, just for information, because the speaker from the audience used the term chronic nociceptive pain. My understanding of chronic pain fits more what Dr. Max described with structural changes, with sprouting and changes in dorsal root ganglia in spinal cord.

Is there a clinical situation of chronic nociceptive pain without seeing those changes?

DR. MAX: Well, the word nociceptors means receptors that pick up noxious stimuli. It's commonly used in pain jargon as either nociceptive pain or neuropathic pain, which means either some tissue damage which rather normal nerve structures are signaling or there's injury to nerve and the pain is something of an illusion.

So nociceptive pain leaves a -- is a very, very broad category that just means viscera or joints or bone is injured.

DR. BRANDT: But with chronicity, with duration, does that not result in changes in structure?

DR. MAX: Well, there are lots of changes. Now we're getting past that to specific mechanisms. For instance, there are many, many anatomical changes if you injure a nerve that I just mentioned, but even inflammation -- Clifford Wolfe's group recently published a paper in Nature and showed that within one day of injecting a rat's paw with a noxious -- with Freund's adjuvant or something like that -- the phenotype of white touch neurons, peripheral neurons, changes, and they suddenly start making substance P, which is a pain -- one of the pain neurotransmitters.

In chronic pain there are some recent papers, one in Lance showing that in chronic degenerative disk disease they now see a network of peripheral fibrous sprouting into the degenerated disk that have lots of substance P.

So, yeah, there are many, many changes, and there are some arguments for differences between pain syndromes. There are some reports in the

literature from UC, San Francisco, for instance, that primary afferents that come from viscera have different -- a higher proportion may have various peptides in them than from joints.

There's certainly not consensus on any of those, even at the basic science level.

CHAIRMAN PETRI: So Dr. Max, can you summarize for us? There's not enough data now to split, but there wills be?

DR. MAX: There is almost -- Yes, there's almost no data. However, there are -- There's a raft of -- There are a tremendous number of very interesting new compounds that industry is developing. There are new animal models and new physiology, and they are going to be in clinical trials in the next five years.

I think, partly, the results of your choice on this will determine whether we get the same old stuff and know very little more about, say, visceral pain or low back pain or whether there's incentive to go in and do that, because if a company wants to go into a study of, say, neuropathic spinal pain, the first study may be a complete bust.

There is no model for them to follow. They may waste half a million dollars or a million

dollars unless there's going to be some reward for them. So to get into all these issues to see if uterine pain is different from gut pain is different from bladder pain, various neuropathic pains are different, there needs to be some incentive.

I think industry may lead the way in this, because, you know, NIH needs some developing process to get into this area.

CHAIRMAN PETRI: I'm not sure that we're reaching any kind of conclusion. It seems very clear that within a few years there wills be more data. Isn't it possible to have such an indication ready and waiting for that data? Dr. Koda-Kimble? Dr. Fernandez-Madrid?

DR. FERNANDEZ-MADRID: This is a very difficult question, and I think addressing the question of acute versus chronic pain -- I believe that from the clinical viewpoint they are different. I think I would support what Dr. Brandt said about osteoarthritis.

Even in osteoarthritis, it is not enough to say osteoarthritis. The natural history of the disease tells us that -- the patient may have many years of osteoarthritis with intermittent symptoms. The intermittency of the symptoms have relevant -- are

relevant for the design of the trials.

In stage three or four osteoarthritis, the symptoms will be clearly permanent and related to weight bearing or effort and so forth. I think this is a completely different problem.

In rheumatoid arthritis I think inflammatory pain, when the patient is active, it's completely different from the pain that the patient experiences in stage three or four disease, that it is there all the time and will not really disappear. So this behaves in many different ways, different from the acute pain.

Now there are -- The unrestricted general pain model is appealing, first because there is no really data to support splitting. Second, the specific indications that you mentioned may be artificial, and also we have to consider that in the treatment of pain we are dealing with a patient, and the patient is not a test tube.

We have many ways to treat pain in addition to pharmacologic agents. We treat patients' pain with heat, with electrical stimulation, with injections, with antidepressants, with a variety of different things.

So I think this is a very complex thing.

I would be inclined not to split at this time and to approve drugs or continue to using drugs in an unrestricted form, letting the medical profession and the patients, the consumers, to decide what drugs are good for what conditions.

CHAIRMAN PETRI: Let me challenge Dr. Max again, though. We're going to be able to split in the future. There is going to be an incentive if those indications are out there to allow people to split and have an indication for different kinds of pain.

Why not try to set up that kind of thing now?

DR. MAX: Well, I guess my concern is would granting a drug an indication for chronic pain decrease the incentive for, say, that company to do more studies in adventurous models or would it decrease the market. If a company is spending $200 million a year to promote their drug for chronic pain and say give it for everything, would it detract from the market for a company that went out and studied, say, bladder pain?

CHAIRMAN PETRI: Well, I guess I'm asking don't we have to start somewhere? Dr. Simon.

DR. SIMON: I kind of wonder if this is not the same question as writing a tax law to create

social policy. You know, are we going to actually write or recommend regulatory environments that are going to encourage industry to look at some very important questions that are biologically very interesting and to help us understand more about that kind of pain?

In asking that question, I wonder if I want to get back to the issue of, if we -- Isn't one way of asking this question by saying, well, what about durability of response, so that whatever your methodology is that you're using to ascertain pain relief, if you measure it at the beginning when it relates to acute pain and you measure it constantly over a six month period to determine by patient analysis it's the same response in that patient in a chronic situation, then that would really give you the same kind of answer without trying to drive industry to do things that perhaps they are not that interested in doing as opposed to what the NIH should be doing.

So I'm a little concerned about that, and I would like some advice and education from people who think about this as to whether or not a durability of response study might not give us the same kind of information in the chronic situation that acute studies give you in the acute situation.

CHAIRMAN PETRI: Okay. Does Dr. McGrath have a comment?

DR. McGRATH: Just again that I think right now to take the label chronic pain, to me, and use that as a claim if something has been shown to be safe and effective for one particular type of chronic pain is misleading.

Chronic pain -- I'm not sure that we even all mean the same thing by chronic pain. I assume we mean a time -- unlimited pain, unlike the pains that we had tried to talk about this morning being time limited, being presumably a symptom of tissue damage that would lesson naturally.

We're now talking about a long term pain that maybe do, regardless of the site -- for example, low back pain, that may be due to a number of different systems' interplay and a number of different mechanisms.

So my concern would be to take one type of chronic pain with one particular set of mechanisms and then generalize that that product would be safe and effective for anyone with un-time limited pain would be somewhat misleading. That's my concern about the dichotomy.

CHAIRMAN PETRI: But our current system is

also misleading, because our current system would suggest that things that are approved based on acute pain trials are going to work for the different kinds of chronic pain.

Are we getting closer to the truth in terms of basic science by starting to split? Well, we all understand there are probably many different kinds of chronic pain, but should we start that splitting process?

DR. MAX: Well, one important difference is that it's clear that the two main classes of drugs that are covered by the existing situation, NSAIDs and opioids, happen to have very broad spectrum activities, that they work on many kinds of pain; but the drugs that are being introduced in clinical trials now, like substance P blockers or South Sea snail toxins, konotoxins, or a variety of other drugs -- there are many drugs with very specific mechanisms that may not have this broad spectrum activity, and it may be wrong to assume that they do.

I mean, to give you an example of a danger in even a smaller category: If I were advising a company for a study on neuropathic pain and you let them do, say, one diabetic study and one post-herpetic study and get a general neuropathic pain category, I

would advise them to send their detail men out and try to market the drug for radiating pain from spinal disease; because there are ten times as many or 20 times as many patients.

That would be totally spurious and not based on fact. So there are many cases -- The tricyclic antidepressants work for several kinds of neuropathic pain, but have been completely ineffective in six studies of low back pain that's not radicular.

You know, there's no evidence of effectiveness for them in acute surgical pain. So I think we need to be a bit agnostic and ask to see the data.

CHAIRMAN PETRI: Well, remember that Dr. Hyde has not limited us on splitting. I mean, I think our first question is to split or not to split, and if we're going to split, you know, how many nodes are we going to have.

There's no reason why we couldn't split off radicular pain from peripheral neuropathic pain.

DR. MAX: You know, I would go for general neuropathic pain category, if you included one radicular and one other. That sounds reasonable to me.

CHAIRMAN PETRI: We have a few people who

are silent here. Dr. Liang.

DR. LIANG: I was afraid you would call on me.

I think that we're saying there is no data or perfect understanding of mechanism. So we're back at, I think, the goal of trying to call the same thing by the same name so that we could discuss it, subset it, blah, blah, blah.

So it really doesn't matter to me how many axes you want to define it, but I think that intuitively there's pain, and then you want to describe it in many ways. One of the, I think, critical ways -- one of the critical dimensions or axis of description is how long it is, whether it's remittent, constant. Those are all, I think, common sense terms that we could operationally define and just get people to use the terminology in the way we define it until we know better.

We shouldn't let perfection be the enemy of the good. We should get it on paper, live with it for a while, do some studies, etcetera, etcetera. I don't think talking about it is, you know -- At some level, at some point, we may be able to define these truly by underlying mechanism. That's, you know, the dream, but you know, even before we knew about

diabetes as an autoimmune disease, we talked about polyuria, polydipsia, polyphagia. That was pretty good, you know, because it's relatively homogeneous groups.

Then we got to the level of understanding, you know, the pancreas and the beta cell and so forth. So I think we're at the level of phenomenology and that we shouldn't make a big deal out of it, but we should do it in a way that we can all talk about the same thing.

CHAIRMAN PETRI: Dr. Laska.

DR. LASKA: I wanted to make two points on Dr. Solomon's question about long term -- issues of long term studies and isn't it enough to see if it works over time.

It's curious that for pain that lasts for a long time -- call it what you like, chronic or otherwise -- what you really end up studying are the compliers, and among the compliers the response rate is high. You can't tell anything from anything else.

You tell the effect of a drug against placebo, because of the early dropouts. Then the inference is on these data items that are extended out under the assumption the response never would have gotten better is what will enable these analyses to be

completed.

In reality, you're not seeing differences because of this problem.

Second, I think there is a difference between the question of whether a general analgesic can be called an analgesic for chronic pain than the question of a particular substance that's useful in one minor area and the question is whether or not it's a general analgesic for the two ends of the spectrum.

I think the easier one is whether chronic -- whether drugs that have been shown to be acute general purpose analgesics in the acute area -- can they be labeled for chronic use independently? That's one, I think, more easily addressable.

CHAIRMAN PETRI: Any comments from our industry representatives in the audience? Splitters?

Now I think -- Seeing none, I think it might be useful to go around the table and have people tell me whether they're a splitter or a lumper, and a very brief explanation why. So let me start with Dr. McKinley -- sorry, Dr. Brandt.

DR. BRANDT: I'm a splitter.

CHAIRMAN PETRI: If you can move the microphone a little bit closer.

DR. BRANDT: I think I would advocate

splitting, because I think these conditions are -- I don't have confidence that what is effective in one situation is going to be effective in another, a lot of because of the ignorance that we have about these. So I'm reluctant to simply generalize with the assumption that this is going to work across the board.

CHAIRMAN PETRI: Thank you. Dr. McKinley-Grant.

DR. McKINLEY-GRANT: I would say I'm a splitter. I think the disease -- We have to really look at the diseases that are causing the chronicity of the pain, and so you get the acute pain and the chronic pain. They may be really different diseases, and I think the neuropathic pain is in a different category, too, of being more of a chronic.

So I would say I was a splitter.

CHAIRMAN PETRI: Dr. Tong.

DR. TONG: I'd be a splitter on this situation here. I'm thinking about -- In the over-the-counter situation, I might tend to be more of a lumper, but I think we're talking about some very specific issues here that doors are going to be opened, and we need to be exploring them.

So over-the-counter, I'd be a lumper. I

think prescription-wise, I'll be a splitter here.

CHAIRMAN PETRI: Dr. Callahan.

DR. CALLAHAN: I'm a splitter, and for the reasons that were stated before about the real differences in the time, unlimited as with acute versus chronic pain.

CHAIRMAN PETRI: Dr. Fernandez-Madrid.

DR. FERNANDEZ-MADRID: For the reasons that have been mentioned before by my predecessors, I'm a lumper.

CHAIRMAN PETRI: Figure that one out. Dr. Koda-Kimble.

DR. KODA-KIMBLE: I'm a splitter for the reasons of different pathophysiologies, but also because I'm concerned that in chronic pain these drugs are going to be used repetitively and chronically, and I'm more interested in toxicity and what those effects are over time.

DR. PUCINO: Frank Pucino. I'm a splitter also, mostly because we already have agents like ketorolac that we've already categorized as acute pain. So we set the precedent for the acute setting. Why not the chronic?

CHAIRMAN PETRI: I'm a splitter, for the basic science reasons, and I'm willing to keep on

splitting every time basic science teaches us something more about chronic pain.

I'm also a splitter, because I want to encourage industry to develop drugs in this area. The greatest frustration that I face as a rheumatologist right now is the treatment of fibromyalgia. We need help, and if splitting is going to give industry an incentive, I'm all for it.

Dr. McGrath.

DR. McGRATH: It may be this corner of the table, because I'm coming full circle -- maybe the water.

I'm still a splitter basically, but I really appreciate the comments everybody has made, but in particular a potential solution to the problem that could integrate lumpers and splitters.

If we look at the acute pain model, one of the features that we use to try to lump things together was that the main issue was pain severity. We knew it was time limited, and we talked about mild to moderate pain as probably being the relevant dimension for lumping together products that would help time limited pian.

I'm wondering if what we can do is help to sift out the relevant dimensions of chronic pain and

look at lumping by those categories which would put us a little bit ahead of having to wait for lots and lots of new data, because we already use those pain features in diagnosis, etcetera, and it would be a starting point.

So I'm both right now.

CHAIRMAN PETRI: Dr. Simon.

DR. SIMON: We're not around yet. I think that I continue to believe that there are differences between acute and chronic pain, that they are hard to measure. We participate in osteoarthritis pain trials that are different than dental pain trials.

So I think that they are doable, and they're distinguishable. I think the safety issue is a critical point, particularly as we're now confronting several of the nonsteroidals that are being used as for specifically pain, and finding long term use is extremely dangerous as opposed to acute sudden use and one time use.

I also believe that neuropathic pain is very different. I'm frustrated by that equally as much as Michelle is frustrated by fibromyalgia. Thank God, I don't see as many patients with fibromyalgia.

Then fundamentally, I'm not sure we should be doing social policy here, and I'm not sure that we

shouldn't let the marketplace, the NIH, the science drive the issue and not regulate that particular issue.

There will be companies developing products for indications, because the market is there, and I don't think it needs to be a regulatory issue. So a splitter, chronic versus acute pain. I think neuropathic pain is an excellent dropoff point for that, in particular, and I'm particularly driven by the toxicity issue.

CHAIRMAN PETRI: Dr. Tilley.

DR. TILLEY: I guess I feel I don't have sufficient data to answer this question, and I would tend to really -- There's nothing to preclude, as I understand, a manufacturer from making a claim for a specific disease now, if they wish to do that; but I would have to see that kind of splitting mandated, given what I'm hearing.

There's still sort of, you know, not a lot of good evidence as to how to do the splitting effectively.

CHAIRMAN PETRI: Dr. Liang.

DR. TILLEY: I guess it makes me a splitter someday, if there was a way to do it, but right now I just don't see it, and I would hate to

mandate a policy without data that would make it useful.

CHAIRMAN PETRI: Dr. Liang.

DR. LIANG: I will split into four lumps, which is that I would omit any descriptor that implied mechanism unless we actually knew. My lumps would include roughly some notion of intensity of the temporal profile of this noxious symptom, the duration, and then yes or no, whether there's a clearcut stimulus and whether it's time limited.

CHAIRMAN PETRI: Ms. Malone, can you take this from the consumer's point of view? Does the consumer want us to split or lump?

MS. MALONE: Well, from my own experience with both chronic and acute pain, I find that the medications that I would use for in exacerbation would just be too toxic to be using for chronic pain.

So I think you need to split.

CHAIRMAN PETRI: Dr. Moreland.

DR. MORELAND: I'm a splitter. I won't reiterate the reasons, but I in general agree with the reasons for splitting.

CHAIRMAN PETRI: Dr. Max.

DR. MAX: I'm a splitter for now. I think there are some issues that would need to be thought

through. For instance, if you only approve a drug for, say, interstitial cystitis pain and it's probably good for lots of things, will doctors be able to -- will patients be able to get it paid for?

There are reimbursement issues as well that might play into this, and I don't know how they fall out.

CHAIRMAN PETRI: Dr. Laska.

DR. LASKA: I would second the last remark. I think it's not a good idea to label something specifically for an indication when it's a general analgesic. One can advertise it and make it sound like it's special to this problem, and that would be a mistake.

So I don't think a classification of splitters or lumpers is relevant until the issue before the house comes to the floor. For those kinds of cases, I don't think you can split. It would be wrong, but for others I think it's essential.

CHAIRMAN PETRI: So you're somewhat of a splitter?

DR. LASKA: I think it really depends on the question, on the two sides. A drug that only works for one indication has to be split out, whether it's chronic or acute, and a drug that works for many

or most, it would be wrong to simply get a claim for one of those indications.

CHAIRMAN PETRI: Dr. Blewitt.

DR. BLEWITT: Well, just speaking for chronic pain, I think that there's a paradigm in acute pain in terms of what the agency has concluded as to the way these drugs are studied.

You can use a model such as dental pain to support a general pain claim, but they have deemed that specific studies in headache and menstrual pain are necessary if you want to make that claim. I can see that that could be done as well.

I guess I'm kind of a cautious splitter, and I'm speaking, I guess, more for myself here. In chronic pain it sounds from what I'm hearing from the experts that there are obvious differences in chronic pain, but that many of them are also alike.

It sounds like neuropathic pain is different than chronic neuromuscular pain and visceral pain. So, you know, there may be differences there, but the agency can look at these again on a case by case basis and determine whether, based upon the known or perceived pathophysiology of these entities, specific studies are needed in those cases.

It would seem to me that there can be a

paradigm for general chronic neuromuscular pain such as the osteoarthritis model.

CHAIRMAN PETRI: Thank you. Dr. Hyde, let me ask you, are you copacetic? Have we discussed question 1 to your satisfaction?

DR. HYDE: Yes, I guess I'm still a little -- Let's just take a specific scenario then to make sure I understand the sentiment.

Say we got, you know, the traditional minimal application for an analgesic, you know, a few acute studies, some chronic safety data maybe with sort of a wishy-washy efficacy aspect to it, comparing it to something. What would the committee think would be the appropriate indication to give that then, just an acute pain claim? Is that what I'm getting from this?

CHAIRMAN PETRI: Should we ask for a show of hands? How many think that that particular application should only be approved for acute pain? Those who agree acute pain only, please raise your hands. Those who think it should still get a general pain indication, if the only studies are acute, please raise your hands.

So there's your answer.

DR. TILLEY: Some of us abstained from

that.

CHAIRMAN PETRI: Well, yes.

DR. HYDE: All right. Then say one particularly studied, you know, say diabetic neuropathy or something, you know, to give it that claim. I guess sort of sentiment, even though people are saying that they're lumpers, I'm not quite sure I got that dichotomy there.

I guess are there any -- Currently, the sentiment then is that most would not really grant a general chronic pain. It would have to be for specific entities. Is that what the sentiment of splitting was?

CHAIRMAN PETRI: Well, I think we're saying that we're cautious splitters, that we expect the data to become forthcoming to allow you to split based on basic science.

DR. MAX: I would add, I think -- I would say I would give a general neuropathic claim if they did one study in spinal radicular pain and one study showing efficacy in something else, in peripheral diabetic neuropathy, post-herpetic neuralgia.

CHAIRMAN PETRI: Now that's actually getting to question 2. So let me read question 2 for everyone.

What study designs and study details should be required in terms of number of studies, pain models, duration of study, etcetera, to support efficacy and safety claims for the pain indications as listed under question 1?

So I think we felt pretty comfortable splitting neuropathic pain. So, Dr. Max, you feel that that should be split again into, shall we say, radicular and other?

DR. MAX: Well, I think it should be split into the standard diagnostic category which peripheral symmetrical diabetic neuropathy is one category, HIV related neuropathy is another, post-herpetic neuralgia. There are many common diagnostic categories which -- This really needs to inform the clinician who is prescribing.

So I think it should be the terminology they are using. As I said, if one wants a general neuropathic pain category, I would include a radicular pain, because that would be new territory, and it would encompass the largest group of patients.

CHAIRMAN PETRI: But what if they did not have a successful study for radicular pain? You would still want to allow them -- right? -- to get the neuropathic indication?

DR. MAX: No. No. No.

CHAIRMAN PETRI: Well, what about all those diabetic neuropathics out there who need a new drug?

DR. MAX: Then they could get -- Then they should do a study in diabetic neuropathy, and it will get approved for diabetic neuropathy.

CHAIRMAN PETRI: Okay. So you're going to have a general neuropathic indication, and that would have to include radicular?

DR. MAX: Yes.

CHAIRMAN PETRI: And then you would have a specific one. Perhaps you would have a radicular only, and then the disease entity only. So we're really splitting here.

DR. MAX: This debate has been -- There are about 50 published trials in various types of neuropathic pain. So the database for non-opioid, non-NSAIDs in neuropathic pain is way bigger than the database for fibromyalgia or visceral pain apart from dysmenorrhea. But that's still -- It's still a big leap.

CHAIRMAN PETRI: Okay. So discussion about this neuropathic indication. Dr. Liang.

DR. LIANG: Well, actually, this is not

completely --

CHAIRMAN PETRI: Microphone, please.

DR. LIANG: I think we're doing some magical thinking here. I mean, most people with chronic pain, irrespective of mechanism, will usually get some acute pain drug at some point or in addition to whatever they're being tried for chronic pain.

I would imagine that, you know, it's a tough enough problem that any indication for anything that sounds neuropathic will be tried in all the other conditions, irrespective of what we put on the label, and I would think that's appropriate. It's a trial and error thing that the individual patient and the physician have to decide. So --

CHAIRMAN PETRI: But do you support the idea of having a neuropathic pain indication?

DR. LIANG: Yes, but I wouldn't go down -- I wouldn't drill down saying that this is only allowable for a diabetic --

DR. MAX: Well, I'm sorry. We're not saying you can only prescribe it for diabetics. It's just that, if the only study is in diabetic neuropathy, I would not want the FDA to sanction they're promoting a drug for every kind of neuropathic pain.

CHAIRMAN PETRI: Dr. Laska.

DR. LASKA: I think it's instructive to review the history of the OTC indications and where that came from. There was a time when you just had to produce two studies in any pain model to show that the analgesic beat placebo to get an indication. Then we started debating -- this debate has gone on for many years among the analgesic guidelines people -- what else did you need to show. I mean, after all, it's not enough, just any two studies in any pain model.

So there was a more definitive approach taken, and that has emerged in the last go-rounds to now we need three claims of pain, dysmenorrhea, headache and some other kind of pain.

Now I wonder whether there's too many drugs that have come out on the marketplace or have been studied in which all three were really required before you could draw the inference that that drug was a general analgesic.

The more hurdles that are put out, the harder -- that are put in front of a drug company to get a drug approved, the less likely anybody is willing to make that investment. Before you now start throwing one more pain type after another to be able to say something is a general analgesic, the less

likely you're going to get good drugs. It's too costly to make this kind of investment.

I think the evidence has to be on the -- the shoe has to be on the other foot. Before you demand a particular kind of pain be studied, you have to argue whether that pain is different, and maybe you exclude indications in a labeling rather than say the other way around, you must study it.

CHAIRMAN PETRI: This could be an extra hurdle, couldn't it? Someone could have the indication for general pain, and then could further show that their drug has efficacy for neuropathic pain. So I'm not suggesting that this be an either/or.

Dr. Simon.

DR. SIMON: One dissenting possibility would be an indication for general pain based on X number of trials that we all would agree on, but why should there be an indication for yea or nay regarding neuropathic pain?

Instead, it would -- the marketplace would decide that unless it was a safety issue, and then because of the issue that it won't be used in neuropathic pain if it doesn't work. Why would the regulatory issue require proof of it working if, in

fact, it works in other painful areas?

We have that circumstance now. I mean, we use drugs in various different ways. Again, do we want to use the regulatory environment to drive people to do the studies because we're biologically interested in them?

I'm very biologically interested in it, but I'm not entirely sure I want to use the regulatory environment to get those studies done.

CHAIRMAN PETRI: Dr. Max wants to reply.

DR. MAX: Yes. I disagree with your strategy of letting the marketplace decide about chronic pain. I find it -- The placebo response is so high, and I've found it so difficult to understand that that -- I'll give you an example.

I have no idea whether NSAIDs are of any benefit whatsoever in neuropathic pain.

DR. SIMON: Oh, I do. Now I don't use them anymore, because they don't work. So the reality is that I didn't need to have a clinical trial prove that to me, and that's my point. I'm not suggesting that you don't have a bar, but I'm suggesting we shouldn't use the regulatory environment to get an indication for a subset kind of pain.

The populous will decide that. Physicians

and health care providers may or may not use an analgesic under certain circumstances, because it just doesn't work.

CHAIRMAN PETRI: Lee, I'm going to strongly disagree. I'm in favor of clinical trials, because although we can learn through clinical experience, it takes us a long time.

DR. SIMON: Michelle, I'm not against that.

CHAIRMAN PETRI: The consumer is going to have to go out there and buy six or seven different things.

DR. SIMON: Michelle, I'm not against clinical trials. I want the clinical trials to be done. I'm just not sure the regulatory environment should stimulate those clinical trials to be done. That's my only point. I'd love to see the clinical trials.

CHAIRMAN PETRI: Dr. Weintraub.

DR. WEINTRAUB: One of the things that will help -- and I'm going to be like a pseudo committee member. You know, I threw off my jacket. I'm a committee member.

CHAIRMAN PETRI: Are the other committee members supposed to take off their jackets?

DR. WEINTRAUB: I changed a little bit. But tell me this, Mitchell. Up to now, the only drugs that work in some of these syndromes that we're talking about, particularly neuropathic pain, are not traditional analgesics. They are not general analgesics. They are not.

I mean, they're anti-epileptic agents, anti-depressants. They are old drugs for another -- for something else in which will get their indication. But among the newer ones, you could probably tell me much better than I can tell you, are there any traditional analgesics that will give general effects on pain where they should be giving general -- should be treating neuropathic pain, diabetic pain, etcetera, etcetera, etcetera?

DR. MAX: Well, it looks like opioids -- There are a number of big studies going on, but so far from the published data it looks like opioids relieve neuropathic pain. The old Hood database estimates that in cancer pain about 75 percent of the efficacy shown in neuropathic pain has been shown in bone pain or other pain.

NSAIDs -- there's just one single blind study in diabetic neuropathy of ibuprofen and sulindac. A problem of clinical experience is the

best of these drugs -- there are about six or eight classes I've looked at. On the average, they reduce pain 20 percent compared to the pain at the end of the placebo period.

So it's such a modest effect. These drugs are also mediocre. It's really tough for even the experienced clinician to get a good impression when the placebo response might be 40 or 50 percent. At 20, it's tough, but for the most part, you're right. There are mostly nontraditional analgesics that have been looked at.

DR. WEINTRAUB: And the newer ones, too, or not?

DR. MAX: The newer ones are -- you know, all sorts -- Well, you're hearing about them in your pre-IND meetings. Yes. I mean, for instance, there are big -- Many drug companies are interested in sodium channels, because these sprouts now have an abundance of sodium channels that are trying -- a number of companies are trying to get peripherally selective sodium channel blockers to shut this off, because the general lidocaine affects brain and heart, and it's too dangerous. Xylocaine is too dangerous.

So there are some very specific drugs that take advantage of specific changes in that model. On

the other hand, there have just been two studies with gabapentin in diabetic neuropathy and post-herpetic neuralgia worked again about 20-25 percent reduction in pain compared to placebo, and there is some evidence that has some general action at the spinal cord gate. Anything, injury, inflammation in rats that tunes up the gain that causes hyperalgesia is reduced in some non-opioid way by gabapentin. I haven't seen published acute pain studies.

So there are examples of things that may be general and may be very specifically tied to the anatomy.

CHAIRMAN PETRI: So again the topic that's on the table right now is whether we're ready to recommend a general neuropathic indication based on one study of radicular pain and one study on other neuropathic pain. Other discussion?

I really don't know where the committee is standing on this. So I think I'll go around again and ask people to give me their individual answers. Dr. Brandt.

DR. BRANDT: Yes, I would give a general indication for those two.

CHAIRMAN PETRI: Oh, so you're in favor of a neuropathic indication, one study radicular, one

study other. Dr. McKinley-Grant.

DR. McKINLEY-GRANT: I have a question. Does -- Do we have to give an indication before the pharmaceutical companies can do studies?

CHAIRMAN PETRI: No, of course not.

DR. McKINLEY-GRANT: Okay. I mean, it seems like I feel like I'm in a very awkward position of, you know, deciding this. I mean, I think there's definitely a need for studies for neuropathic pain. I mean, we have a -- but like Mike was saying, many of the drugs are not analgesics, at least the ones that we've used so far.

So I think studies need to be done for neuropathic pain. Let me put it that way, and that drugs need to be developed.

CHAIRMAN PETRI: Dr. Tong.

DR. TONG: I agree with Dr. Grant and Dr. Brandt.

CHAIRMAN PETRI: Dr. Callahan.

DR. CALLAHAN: I agree that studies need to be done.

CHAIRMAN PETRI: Dr. Fernandez-Madrid?

DR. FERNANDEZ-MADRID: No.

CHAIRMAN PETRI: Dr. Koda-Kimble.

DR. KODA-KIMBLE: I support studies for

neuropathic pain.

CHAIRMAN PETRI: I see how the question got changed here.

DR. KODA-KIMBLE: Well, I mean I'm presuming this is not the hurdle to get a drug approved or something. I mean, they might be, you know, approved for general analgesia, but if they did these specific studies --

CHAIRMAN PETRI: You would allow a separate indication?

DR. KODA-KIMBLE: -- a separate indication. Yes.

CHAIRMAN PETRI: Thank you. Dr. Pucino.

DR. PUCINO: Yes, I agree.

CHAIRMAN PETRI: I'm in favor of a separate indication for neuropathic pain. Dr. McGrath.

DR. McGRATH: I'm in favor, and I think the criteria that were proposed are very reasonable and appropriate.

CHAIRMAN PETRI: Dr. Simon.

DR. SIMON: I'm in favor of neuropathic studies being done. I don't understand the criteria that need to be applied to determine whether they're successful or not, and I'm still not entirely sure

that we should be using this as an indication to get them done.

CHAIRMAN PETRI: Dr. Tilley.

DR. TILLEY: I agree with Dr. Grant and Dr. Madrid.

CHAIRMAN PETRI: Dr. Liang.

DR. LIANG: I'm in favor of apple pie studies for pain.

CHAIRMAN PETRI: Ms. Malone.

MS. MALONE: I think studies need to be done if you're going to indicate it for neuropathy.

CHAIRMAN PETRI: But as a consumer representative, you would be in favor of a separate indication for neuropathic pain for drugs that maybe did not pass the general pain indication?

MS. MALONE: Yes.

CHAIRMAN PETRI: Fine. Dr. Moreland.

DR. MORELAND: I agree with the separate indication for neuropathic.

CHAIRMAN PETRI: Dr. Max.

DR. MAX: Yes.

CHAIRMAN PETRI: Dr. Laska.

DR. LASKA: It's always good to have studies.

CHAIRMAN PETRI: Dr. Blewitt.

DR. BLEWITT: Well, I don't choose to comment on the specific study requirements, but as I said earlier, it does sound like it's a different kind of pain.

CHAIRMAN PETRI: Now let me open this up for other study designs. Are there other areas where people feel ready to suggest a study design or study details? Dr. Max.

DR. MAX: One thing, it may be that when people try to do studies -- When we were talking about chronic radicular pain, acute radicular pain is a completely different kettle of fish.

It may be that people -- drug companies will go out a few years from now and find you just can't get these studies done. Drugs are great in diabetic neuropathy. It seems to work for lots of patients, and this is a rotten population. I mean these could be reconsidered if it is a dumb idea.

CHAIRMAN PETRI: That's called progress. Dr. Simon.

DR. SIMON: But the problem is you can't really reconsider, once it's a regulatory issue. It's a very difficult supertanker to turn around. That's the dilemma of getting into the regulatory environment, and so, therefore, I caution everyone who

is supporting indication issues from that point of view.

Yes, doing the trials is great, but I want to ask a question about osteoarthritis, because it seems to me we've sat around this table and I've participated in studies looking at signs and symptoms of improvement in osteoarthritis.

To me, pain is a symptom of osteoarthritis, and to me those studies are typically long term, relatively speaking, compared to dental pain trials, and thus perhaps, to me, that's a chronic pain study. Maybe it's not, but I think it is.

So it seems to me, we've got plenty of models out there for looking at chronic pain in other situations. These drugs have been indicated for pain relief.

I think that the environment of new drug development, like Dr. Weintraub suggested, would generate all of the efforts because of the issues regarding the marketplace, the interests of how many patients who are out there with neuropathic pain who are not being made better, and industry would be well advised to address that issue so that they can enrich their coffers and make their stockholders happy.

So all of that is going to drive all of

this. What's not going to drive this is a regulated environment that's going to drive everybody crazy and can't be changed easily as things go on.

CHAIRMAN PETRI: Well, let me ask Dr. Hyde to respond to that.

DR. HYDE: Okay. Well, I think it's not so much a matter of what we would require. It's what we wouldn't grant in response to something. You know, if someone were to study a specific entity -- I mean, we would have to recognize that, if it made sense.

So the idea of, you know, a neuropathic indication -- I guess our question would be how much would we generalize within that category. I mean, if you did two diabetic neuropathy studies, you know, we would have to say it works for that.

The question addresses, you know, how general could we make at least that category? Can we study a couple of representative types and maybe make a broader claim? So that's useful.

I guess one question I'd like to, you know, put to the committee: If there were to be a general chronic analgesic, you know, we wouldn't -- I think we could identify a category, that we wouldn't necessarily require it working in a neuropathic model, but it would be recognized that, you know, it was

limited in some way in what we meant by the chronic analgesic or chronic non-neuropathic pain or chronic, you know, somehow or otherwise limit it.

The value of this -- In some ways there would be some incentives. Another consideration for us, although not all that great a scientific issue, is the advertising aspect of it. If we don't have anything in particular that we would require for an indication, we're sort of hard pressed to say you can't claim it.

You know, if you currently have the pain indication and you go out there and say this is, you know -- use it in your neuropathic; this is a patient profile and would be a good patient for our drug. We're not in a good position to say, well, you know, no, you can't, because this is pain. It's indicated for pain.

Our argument is a little weak. If we able to say, well, you know, here's our neuropathic indication. We have a guideline for that, this is what it means to be effective in that. Then our position is a little stronger. That may not be a great consideration for this committee. It's not a particularly scientific one, but that's one of the issues we have to deal with, too.

CHAIRMAN PETRI: Other committee suggestions about other specific study designs or study details? Let me ask Dr. Max: Within your neuropathic indication -- I'm attributing it to you now -- how long should the studies be?

DR. MAX: Well, one issue is should you allow single dose studies. There are some published studies, for instance, of intravenous infusions of opioids or oral administration of opioids or intravenous local anesthetics relieving neuropathic pain.

I'm a bit suspicious of that, because a lot of the neuropathic pain, for instance, is much more realistic when you're out walking around than lying on my table in my laboratory with an IV in your arm. So there are tremendous placebo responses.

I would really rather see -- Generally, I mean, I would rather see a couple of weeks. There's evidence to suggest that the most sensitive study as outpatients requires about a week of measurements average. Then you need the amount of time it will take you to titrate the patient up to an effective dose, which might be a week. It might be two weeks. It depends on the drug.

So I would suggest that the titration time

-- The length of the study should be the titration time plus a week for the best efficacy measurement.

CHAIRMAN PETRI: Other thoughts about length?

DR. SIMON: What about toxicity?

CHAIRMAN PETRI: Dr. Simon has a question.

DR. SIMON: What about toxicity in that, if you're using something in a chronic neuropathic situation -- for example, diabetic neuropathy -- it likely will not get better on its own unless the person loses their leg, God forbid.

What do you think about the length of time to understand the toxicity issue, and I actually refer back to what we now have learned about certain of the newer available analgesic nonsteroidal anti-inflammatory drugs that have no problems in the first 30 days but have big problems after 30 days; and if you didn't do the studies long enough, you wouldn't be aware of them.

DR. MAX: Well, the longer -- I mean, I'd be interested in the most data I could get. For instance, with tricyclic antidepressants, the longest study that's ever been done with them is six weeks, and we've now done a study in AIDS where after eight weeks the pain really goes away, and maybe -- is this

real?

There's always the issue of having more safety data. However, what we really need are drugs for these patients who are suffering, and the more -- the longer the study you require, the harder it is for a company to do a first study to show efficacy and get their capital behind them because of the cost of toxicity studies.

So I think that's -- You know, that's a toss-up. You can't be unreasonable.

CHAIRMAN PETRI: Dr. Liang.

DR. LIANG: I think that's much too short. My toughest patients are the diabetics, SRDS, and post-herpetic neuralgia. Especially with the agents that we're using, which are usually not analgesics, it's not a clear dose relationship with the symptom relief. I'm often diddling with the dose or titrating to the intolerance level.

With tricyclics, you know, that can be one and a half grams, six to 12 weeks kind of thing. So I think that that's much too short. I mean, we may actually miss some effective drugs, especially you can caricature what we do now as a guideline.

CHAIRMAN PETRI: Do we have a consensus? Are we talking two months? Dr. Liang. I'm sorry.

Dr. Koda-Kimble.

DR. KODA-KIMBLE: It seems that the duration would also be determined by the pharmacokinetic and pharmacodynamic characteristics of a drug. I mean, if it has a very long half-life and it takes, you know, three weeks to accumulate, you won't see -- presuming there is a level of response of that, you may not see anything until the drug reaches its steady state.

DR. MAX: In the 1992 FDA guidelines on analgesics they talk about Phase II efficacy studies, and then Phase III studies and other safety studies. So I think one can consider the issues you're talking about in terms of safety as a different tier of studies.

CHAIRMAN PETRI: I am separating that out. Just talking now about efficacy. Should that be two months? Is that a reasonable -- I'm seeing a show of fingers with three.

DR. MAX: I mean, that may be too long. I think, you know, if we could have a drug that worked over a two-week period, I'm satisfied. I wouldn't want to shut the door to --

CHAIRMAN PETRI: No, but you brought up a concern. What if it works for four weeks, and then at

six weeks it doesn't? I mean, do we know enough about neuropathic pain that we can say that, if it's going to work, it's going to work in four weeks?

DR. MAX: No.

CHAIRMAN PETRI: A comment from the audience.

MEMBER OF THE AUDIENCE: Yes. It's Dr. Baboul from Cyrex. The comment relates to duration of evaluation in neuropathic pain.

I think there's a need to separate out the safety needs for approval of the drug. Clearly, some of the comments we were hearing relate to long term safety as opposed to tachyphylaxis, you know, a response to neuropathic pain.

It's likely that most drugs will have analgesia activity that go beyond neuropathic pain and, therefore, these drugs will have in their dossier a substantial amount of long term safety data. I think that's a given. Most companies realize that they will be submitting a dossier containing a substantial amount of safety data.

Efficacy-wise, I think I agree with Dr. Max, that a period of about, you know, a week certainly is sufficient for evaluation of efficacy. However, the problem is that it is often difficult to

ascertain whether you have optimized the analgesia with the drug.

Some of these drugs have dose limiting side effects, requiring a gradual dose escalation. Also, I think clinicians need to know whether these drugs have reached optimal efficacy at the dose that is being suggested.

For that reason, I think that a strategy where you escalate the dose over a period of weeks, depending on tolerability, is reasonable. In a paper that we have in press in Neurology right now, we employed a four-week crossover duration, which is reasonably consistent with what Dr. Max has published in the past and, I would say, is not a substantial departure from what we do in OA studies.

Certainly, there is some discussion about OA study duration being increased for specific claims, but we know that a four-week study, possibly a six-week study, and certainly no more than two months is adequate to establish efficacy.

CHAIRMAN PETRI: Dr. Max.

DR. MAX: Something I'm concerned with even more than the length of the study is dose response. We academics have done almost no dose response studies in any neuropathic pain condition,

and particularly since so far we're just getting about 20 percent relief with each, we're going to need to combine them.

If you do combination studies -- combination treatment on your own, you really need to know the dose response curve. So I would require, whether it's in the same study as efficacy or another study, that you look at least two, three doses, you know, so you really know what the curve looks like.

CHAIRMAN PETRI: Dr. Simon.

DR. SIMON: I guess we do have some information about the length of time from efficacy. If you look at the OA studies again, even the newer ones -- I'm pretty struck by the length of time that still remains of placebo response, even out to six weeks.

So I would actually be much more encouraged by three month studies for efficacy, and I think that that also raises the issue of eliminating the issue of placebo and giving you more understanding about the durability of the response and also the toxicity issue.

I don't -- I'm not applying this to the Phase I-II trials, which can be much shorter, should these dose ranging and other control issues be

important. I think the Phase III trials, however, need to be long enough to get rid of the placebo response, at least as we understand it, as much as possible, and then to give us as much information about durability of response, which I think is important based on this -- I'm not sure it's tachyphylaxis, whatever that is, but this lack of response that sometimes happens.

CHAIRMAN PETRI: I'll summarize where we are on question 2. We really only felt comfortable about expanding the neuropathic indication, and there seems to be some concerns that three months might be optimal for efficacy; but again, it's just for this one specific example and not based on a lot of data.

I think this might be a good time to take a break. So we'll take a 15 to 20 minute break, and then reconvene.

(Whereupon, the foregoing matter went off the record at 3:00 p.m. and went back on the record at 3:18 p.m.)

CHAIRMAN PETRI: The next question we're going to address is number 3. For a pain category which has subcategories, how should the subcategories be studied and replicated to support efficacy claims for the pain category?

Now we haven't actually established a lot of subcategories. So I think we better stick with our neuropathic for this question, which we had subdivided into radicular and other neuropathic.

I think where we left it was we would only require one study for each of these subcategories. Now let me actually ask Dr. Max, is that an accurate representation of how you viewed this indication? You would get the neuropathic indication for one radicular and one other neuropathic study?

DR. MAX: That's what I proposed. Now there's the issue -- What I said was, I think, the crucial issue is dose response, and one issue is are you going to need dose response in each of these categories.

I think it is reasonable one could kill two birds with one stone. You could have your efficacy study be a dose response study. So I'd say yes. If we're concerned that, say, radicular pain has a different pathophysiology than peripheral nerve disease, then the dose response might be different.

So I would want some information about choice of dosing in each of those two.

CHAIRMAN PETRI: Now do committee members feel uncomfortable with this idea that you would only

need one pivotal trial for each, radicular pain and other neuropathic? In other words, shall we have two trials for radicular, two trials for other neuropathic?

Thoughts, Dr. Fernandez-Madrid.

DR. FERNANDEZ-MADRID: I'm uncomfortable with one trial.

CHAIRMAN PETRI: Dr. Pucino?

DR. PUCINO: I agree. One trial for each.

CHAIRMAN PETRI: One trial for each? Okay. So we already have dissension here. Let me ask Dr. Tilley to view this as a statistician.

As we split, you know, we're creating more of a hurdle for industry.

DR. TILLEY: Well, as I said to you at the break, I'm really uncomfortable with this discussion without data. I mean, I really would -- because, for example, one trial or two trials? If one trial is supported by a lot of evidence from other studies that could be reanalyzed for that subgroup, that's one thing.

If the one trial is very short duration, and you really don't know much about safety, then that's another thing. I guess I'm finding it very difficult to come up with some sort of rule here, and

I'm not comfortable with it.

DR. MAX: Here's another to add onto that. What are you going to do with negative trials? You know, if you have one positive trial and one negative trial or one positive and two negative trials, how do you want to handle that?

One solution in the 1992 guidelines which really pertains to efficacy, single dose efficacy studies, is to always require a positive control, a drug that has known efficacy, to test assay sensitivity.

There are some times that we do an assay, and the patients we get or the methods we use just don't work, and if you can't separate, say, ibuprofen from a placebo in this dental study, you just throw in the garbage and don't count it against the drug.

So you might want to make a requirement that you include a standard, say desipramine or amitriptyline in diabetic neuropathy; and if that doesn't show efficacy, you won't count a negative result against you, but if it's just a clearcut negative result without -- then you may need extra evidence to overcome the negative result. But I don't know if we're going to be able to get into these, you know, fine points.

CHAIRMAN PETRI: Let me ask Dr. Hyde. For some of these things like headache, dysmenorrhea, only one positive trial is required. Is that correct?

DR. HYDE: That's for the OTC policy. Only one is required if they first get the core analgesia claim.

CHAIRMAN PETRI: What is the agency's feeling about coming up with a new indication such as neuropathic pain? In general, would you favor two radicular trials to other neuropathic trials?

DR. HYDE: That's been the traditional stance, but as I indicated, as we reevaluate the efficacy requirements, you know, that's something that would be entertained, I think. You know, we'd like your input on that. If we feel diseases are related enough that one really is a form of replication for the other, you know, that would be useful information.

CHAIRMAN PETRI: I think also we always care about the quality of the trial, pivotal trial, multi-center, an active comparator arm.

Let me ask for other opinions about this issue of two versus one trial.

DR. MAX: About the number of the trials, it isn't that arduous for industry when you're talking about the dental model, because one can stamp those

out, high quality dental trials, all day and spend a little extra money and know you've got it.

Diabetic neuropathy studies -- there are a few dozen done, and they have replicated reasonably well. As I say, radicular pain is -- It may be a gargantuan task to get one good looking trial, and it may be asking -- You know, it's scared the companies away up until now and scared the academics away, and asking for more than one may be an awful lot to ask.

CHAIRMAN PETRI: This is especially going to be a consideration for talking about some of these trials being done academically where it may be very difficult to have multiple trials.

Dr. Hyde?

DR. HYDE: Yes. What about the role of post-herpetic neuropathic pain? Would that substitute for diabetic in your mind or --

DR. MAX: Post-herpetic -- As I said, post-herpetic neuralgia has shown exactly the same responses to tricyclics as diabetic neuropathy, but we don't know anything about radicular pain, and general back pain has been negative.

So I would view post-herpetic as analogous to diabetic, that those are two other conditions that are rather small, that have a few hundred thousand

people in the country, and you go in and get an indication for post-herpetic neuralgia alone or you could do a study in each diabetic and post-herpetic and get an indication for post-herpetic and diabetic, or you could do post-herpetic plus radicular and then get a general neuropathic.

The post-herpetic studies are about as well trodden as diabetics, and maybe they're about 50 percent the number of patients around. The patients are older, and there are, you know, more safety concerns.

CHAIRMAN PETRI: I think there's a general consensus that we're close to realization of this neuropathic pain indication. The other things we've talked about, trying to subdivide chronic pain, are going to have to wait until basic science catches up, but let's talk a little bit about that in terms of philosophy.

We thought that maybe basic science will be able to define a myofascial pain mechanism, bone or joint, visceral pain mechanisms. Once the basic science has caught up and we think we can subdivide chronic pain, how many studies for an indication for a chronic pain subcategory? Let me ask Dr. McKinley-Grant. Do you have an idea what you would want?

DR. McKINLEY-GRANT: I'm really at a loss. I mean, I would say one good study should do it, if you're doing these different categories that are -- sounds more connective tissue that you're discussing.

CHAIRMAN PETRI: Well, for example, for myofascial, let's take fibromyalgia. Is one pivotal, multi-center study and active comparator going to be enough or, as we start to make these subdivisions before we really understand -- in other words, have the clinical science caught up with the basic science, let's say, shall we have two?

DR. McKINLEY-GRANT: I'll just abstain on this one. I mean, I would say one. If it's an adequate multi-center clinical trial, it should be adequate for, let's say, fibromyalgia.

CHAIRMAN PETRI: Dr. Tong, with your pharmacology background.

DR. TONG: I think it's the quality of the study. I mean, we've seen many studies presented, poor quality, you know, would never stand the challenge of critique. So I would say one, but more important, quality, the quality of the study, and can we get the expertise to make sure that that quality is assured in the study we see, that we're presented?

CHAIRMAN PETRI: Let me ask Dr. Fernandez-

Madrid to take this example: A fibromyalgia trial. Would you accept one?

DR. FERNANDEZ-MADRID: If it is a multi-centric trial of high quality with a large number of patients and it has adequate power, I would consider it.

CHAIRMAN PETRI: Now our pain experts, Dr. Laska. Do you feel comfortable with one trial when basic science starts to subdivide chronic pain for us?

DR. LASKA: I feel uncomfortable with the discussion. You know, the business about what sufficient evidence is in the FDA is undergoing transition in lots of areas, not just this one.

There's a major, major political as well as scientific issue on this very question on a drug called myotropin for ALS. What constitutes adequate evidence to support a claim is a very serious discussion that requires a little more than opinions. I think they're based wholly on adequate looks at what the databases are in the past, and would be supportive of a historical view that this data was enough, and now that ten years have gone by, we know that data was enough, because it was true.

I'm not suggesting we need those ten years. I am suggesting we need a little more than

we're up to now to have a yes or no going on an issue of this kind.

CHAIRMAN PETRI: Dr. Max, any thoughts listening to this discussion about number of trials required for a new chronic pain subcategory?

DR. MAX: Not that I haven't said.

CHAIRMAN PETRI: In terms of length, if there are chronic pain subcategories, your thought about the length those trials should be?

DR. MAX: Well, as I said, I think that for the purposes of most efficient measurements, you should have a week of daily or twice daily measurements as the primary outcome, and then the time for reasonable titration, and then for a proof of efficacy -- and then I think it's very reasonable to ask for longer trials, as Dr. Simon said, to look at safety and look at durability, but --

CHAIRMAN PETRI: But for your primary efficacy trial, we sort of came to a consensus about three months for neuropathic pain. As we get to chronic pain subcategories, does three months again seem --

DR. MAX: Yes. Again for efficacy, I think three months is twice as long as anybody has ever done a neuropathic pain study. You know, it's

very long. It's very expensive, you know, for the primary efficacy studies, and I think it may impose quite a barrier for companies to get in and do three months worth of toxicology.

So I -- Again, I think that, if I had a week of data showing that a drug worked for visceral pain, it would be the best data that we've had thus far for that category. So I would have -- I would opt for shorter efficacy studies and then, you know, for some phase III confirmatory studies and safety, you could do it longer.

CHAIRMAN PETRI: Dr. Laska.

DR. LASKA: The issue of studying chronic pain over long periods of time and demanding proof of efficacy when the comparator -- to prove efficacy as placebo is a difficult one at best. The notion of getting it through an IRB is a little bit difficult.

So Mitchell's argument to the point of shorter studies to show effectiveness really make sense. It's very difficult to do efficacy trials with a control group as a placebo, which is all you really need. Tough to do.

CHAIRMAN PETRI: So you're arguing for shorter duration?

DR. LASKA: Short term, and you might ask

for another reading at the end where there's no comparator, if that's appropriate, and it may very well be. Is the patient still feeling satisfied with the response? That's a low level science view of what is working or not, but to demand closed blinded clinical trials with comparator drugs that would include placebos is just too tough to do.

DR. MAX: There's a lot of evidence thus far in the literature that patients with lots of care in an academic center where they put a lot of effort into it will put up with three weeks of a placebo up to -- I mean, we lose about ten percent of patients on every six-week study period.

There's no data that people will put up with more than that, and particularly if you try to make it more complex like add an active standard comparator. You know, sometimes people try, say, a standard tricyclic they won't want to be on in the first place, and to ask them to go on it for a long time is going to be impossible.

CHAIRMAN PETRI: Now can you -- the two of you think of an estimate? Are you talking about one month?

DR. MAX: I'd say two or three weeks. If the kinetics of the drug, you know -- If the drug

doesn't have a lot of side effects and you could get people up to their maximal tolerated doses or the target dose in a week, two weeks is fine. I mean, if you want to say three weeks, that's fine, but I don't like three months.

CHAIRMAN PETRI: In rheumatology we have a lot of experience with this chronic pain syndrome called fibromyalgia, and it fluctuates. It would be hard for me in a two-week period to be able to tell you whether the patient was better or not, unless the drug was very dramatic.

So I'm thinking more in terms of one month as a minimum time. Let me ask Dr. Fernandez-Madrid about how he feels.

DR. FERNANDEZ-MADRID: I would agree. The variability of the symptoms in these patients really make a very short trial -- Probably, it would be a failure.

DR. LASKA: I think you're into the question of what models and what clinical trial models will be sensible. It may not be required to do the trial in which you have a double blind -- the comparator treatment all along the way. It may be that after a period of time, you can open up the trial, maybe keep it blinded -- that's not the

relevant point -- but the point is that you'll ask down the road how are you doing, is this drug still working for you, and you demand a comparator with the high tech science in the front.

To know what's going on down the road, you have to use other kinds of techniques. It's too difficult to know.

CHAIRMAN PETRI: Comment from the audience.

MEMBER OF THE AUDIENCE: Yes. I'm --

CHAIRMAN PETRI: Please identify yourself.

MEMBER OF THE AUDIENCE: Yes. I'm Celia Winchell. I am one of the team leaders in the Division of Anesthetics, Critical Care and Addiction Drug Products at FDA, and we have a keen interest in the proceedings today; because we're responsible for narcotic analgesics, and a lot of chronic pain products come to our division.

One of the things I hope that we will not miss the opportunity to mine from the committee's experience is this issue of the amount of evidence -- and we're not asking would one trial be sufficient, but in your experience within some of these subcategories such as myofascial pain, neuropathic pain, inflammatory pain, would there be some specific

diagnoses so similar to one another that one trial in each could be regarded as confirmatory for both.

So that two trials could be performed, but not in identical populations, that would be regarded as confirmatory trials each for the other?

When Dr. Max said in his experience you can't even extrapolate from one viscera to another, those are the questions that the agency needs help with. Are there two conditions so similar that one trial in each could be confirmatory of both?

So I hope we won't let you get away without getting some of that information.

CHAIRMAN PETRI: I think we're going to have great difficulty in addressing your question, because of the lack of data. Let me ask Dr. Max. I think you were suggesting that herpetic neuralgia and diabetic neuropathy perhaps.

DR. MAX: As I said, there are probably five studies of tricyclics in post-herpetic neuralgia and a dozen in diabetic neuropathy showing very similar responses comparing, say, the way SSRIs and mixed serotonin reuptake blockers line up.

There are similar responses of those two conditions to lidocaine intravenously. So there are some similarity -- As I mentioned, one drug we've

tried, dextrominophen, in two successive trials has had discordant responses.

So sometimes -- So one can interpret -- one might interpret that the mechanisms -- that the tricyclics in lidocaine are working on are shared, but the NMDA blockade is not, but that's still a small database.

CHAIRMAN PETRI: So I think the answer is right now we probably can't answer that question.

Let me ask Dr. Hyde. We're working through question 3. Are there other specific things that you wanted to have us address?

DR. HYDE: No. I think, you know, it's helpful to look at the neuropathic pain as a particular. I mean, that kind of helps us as, you know, one possible paradigm that we could look at. I mean the fact that you would consider, you know, certain things to be supportive or replicative of another, you know, gives us something we could, you know, possibly fashion around.

DR. MAX: One additional comment on the one study versus two studies. I guess, once you approve a drug for anything, then it's out on the market and it would be used for -- It's set loose.

So, I mean, one might want to have a

higher threshold, say two studies, for first approving it for anything, and then one additional study for additional claims; but I think, as Gene says, that's a real big issue and needs careful consideration.

CHAIRMAN PETRI: Now to move on to question 4, what study designs should be required to establish the duration or pattern for short term use (acute pain), versus long term analgesics?

Dr. Max, if I could ask you to start in terms of what you believe is necessary for the acute pain indication when we get to this point where it's possible to split.

DR. MAX: Yeah. I don't understand the question of study designs to require the duration or pattern for short term use.

CHAIRMAN PETRI: I think we're asking to wax philosophically here. If you were able to split off acute versus chronic pain, and if there were separate indications for those, what is your --

DR. MAX: Well, generally, the first -- You know, acute -- for acute pain, the only efficacy studies that really have made a difference are single dose efficacy studies up to this point. Then if you ask additional -- companies have been required to do repeated dose studies in those conditions, mainly to

learn how people take the drug, how long they last, what side effects.

I think a bunch of us at the American Society for Clinical Pharmacology and Therapeutics have written three or four pages about how one might do repeated dose studies to satisfy that, but I mean, there are some issues.

There are some drugs where you might want to -- where there are minimal dose related side effects that would impair people immediately, like giving NSAIDs in major surgery where you're not going to relieve the pain, but you're going to take a dent out of it, and you don't -- It doesn't get in the way of narcotics which you give on top of it.

I think it makes sense to give it by the clock in some studies and do dose response studies by the clock with various doses. On the other hand, in small -- in conditions with only a little bit of pain on the second and third days, you may want to use PRN dosing, but it really depends on the particular situation. I mean, it's a very complex question. I don't know exactly what you're after.

CHAIRMAN PETRI: But you would encourage repeated dose studies where it appears appropriate?

DR. MAX: Repeated dose studies are

important for a variety of reasons. You want to see how long it lasts, what the side effects are. You want to get an idea of dose, and I think a fundamental question is whether you want around the clock or PRN dosing.

CHAIRMAN PETRI: Let me ask Dr. Laska again. In this hypothetical world where we've been able to split off acute pain, how do you think study design should be --

DR. LASKA: I think in the area of acute pain there's so much known that there isn't much need to go into further discussion. There is general paradigms which, I think, not only are appropriate but are mandatory.

You've got to really try and characterize the treatment. I myself would like to see more dose response studies where there are multiple doses of one time administrations, but that's a slightly different topic. But when it comes to chronic pain, trying to characterize how a treatment goes as it's used over time, I think, the game changes.

I don't believe it's necessary to do the same kind of acute observations to learn the pattern of the product. Yet we still need some good thinking. My view would be that there is some need for lighter

type questions.

CHAIRMAN PETRI: Telephone survey, for example?

DR. LASKA: Telephone surveys, things of this kind, which will give a general indication when the product and when the drug starts to fail, when it's no longer doing its job, when there is an adjustment to it or when a dose adjustment is needed.

These kinds of questions have been hotly discussed in chronic disease situations where, for example, in depressants the issue becomes, when the episode is over, can I take the patient off this drug or not or is there a danger of relapse.

So the issues are not quite comparable, but they are in some sense. So you really need a lower level of information to know when things start to go wrong, and there some good thinking is still needed to be done.

CHAIRMAN PETRI: Dr. McGrath, can I ask you to address this issue. If we're able eventually to split off acute versus chronic pain, do you have suggestions on chronic pain design?

DR. McGRATH: No. I think -- I don't think I can really add to what's already been said. I think there are some excellent suggestions.

CHAIRMAN PETRI: Dr. Max had a comment.

DR. MAX: I have a few other suggestions regarding chronic study design, and I want to get back to Dr. Simon's question before about what's the dose response. If you give a sedative, will people get pain relief.

I have a concern that, particularly since the best drugs we have now give only about 20 percent relief and the placebo response can sometimes be much more than that, maybe a drug that's -- and if we just allow -- require one study, maybe a drug that just makes people woozy and has no impact on the pain system will in some hands, compared to an inert placebo, look like it relieves pain, and I think we ought to be on guard against approving a toxic drug which has no pain relieving effects because of spurious placebo responses.

So I'd recommend -- there's a really nice paper that Mike Weintraub wrote with one of his proteges, a guy named Mascuchi in Clinical Pharmacology and Therapeutics in about '85 looking at blinding questionnaires.

I would suggest that the company show or at least do their best, because the methodology hasn't been set on this -- do their best to show that this is

not just a side effect triggered response, that they need to look at side effects in the active drug groups and the placebo group, consider the use of active placebos, placebos that contain some active ingredients, and what Mike and Mascuchi were writing about was give a questionnaire to the clinicians and to the patients to see if the blinding is intact.

There are actually some ways -- If patients get relief, they will say, oh, I know I had the real drug, and it looked like the study wasn't blind; but actually, if you stratify the responses and analyze the people who got relief, got a little relief, and got no relief, you can see if you can get a better look at blinding that way.

So I think there needs -- This issue needs to be addressed. Up until now, it really hasn't been, despite calls from academics like that, because people are always afraid if they ask to see if the study was blinded and they find it wasn't blinded, it won't get into a good journal.

So it's rarely done, but I think, if the FDA requires that a look at blinding be done, particularly if you include other active comparators or dose responses of the active -- of the test drug, that may be one way of getting at it; because if your

drug beats another active drug that produces side effects, that relieves your worry.

A final issue is I think there should be some quality of life measures incorporated besides pain, not that a drug should have to show that people's activities improve. It's hard enough to show that pain is better. However, we want to know that the drug does not intoxicate people so much that the improvement in pain isn't worth it.

There really hasn't been much of a track record with quality of life studies in most of the pain studies in the literature. I think the arthritis people have been doing a lot of work on this, but we in neuropathic pain, for instance, we don't know how to do the right quality of life measures.

I think Parke-Davis just had some nice studies of gabapentin where quality of life tracked pain response. So I think this needs some spade work, too.

CHAIRMAN PETRI: Again, the quality of life measures can be administered over the phone, for example. There are some innovative ways to think about doing these studies which are of a large number of patients, but not at a huge cost.

Dr. Hyde, let me ask you, are there other

things specifically here that you wanted us to address?

DR. HYDE: No. I think the discussion has been very helpful.

CHAIRMAN PETRI: All right. I think we're ready to ask Dr. Weintraub if he'd like to summarize today.

DR. WEINTRAUB: First of all, I want to make a small correction to that paper that Mario Mascuchi and I wrote. We didn't call for an active placebo. We discussed the issue of active placebos, and we turned it down, because of a lot of worries about active placebos; but you know, that's a small issue.

This has been, again, another good day on a hard subject. Dr. McGrath and I were chatting before, before the afternoon session started, and she was very excited because this was really good stuff for her. I understand, and I appreciate that we got to talk about some of these issues, admittedly, without much data.

We don't have much direction to give you. We're starting back at the beginning and trying to make the thing exciting. As John -- Well, it's exciting to the people who are involved in this issue,

I hope. But as John said, this is a very -- It's a nascent question for the FDA, and I do think that we got some good information. I appreciate it very much.

CHAIRMAN PETRI: I'd like to especially thank Dr. Max, Dr. Laska, for your help today. I'd like to thank all of the committee members.

We're adjourned.

(Whereupon, the foregoing matter went off the record at 3:48 p.m.)